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Volume 22 April, 1955 Number 4

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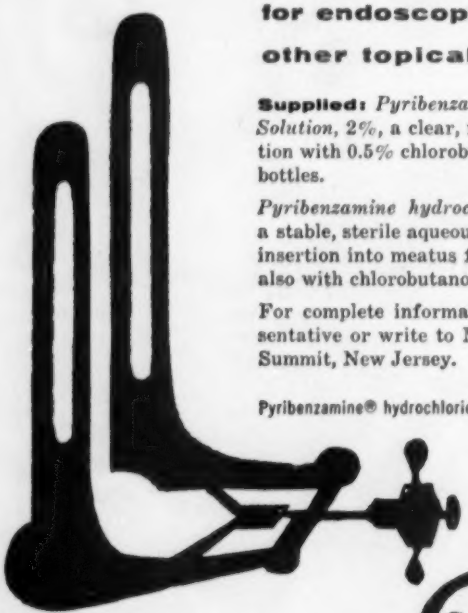

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1. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Prepared with Collaboration of the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Baltimore, Waverly Press, 1952.

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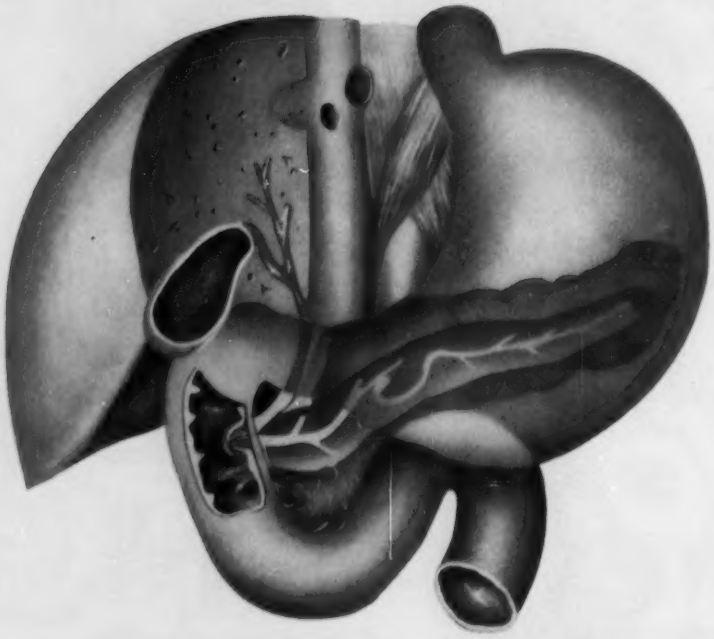

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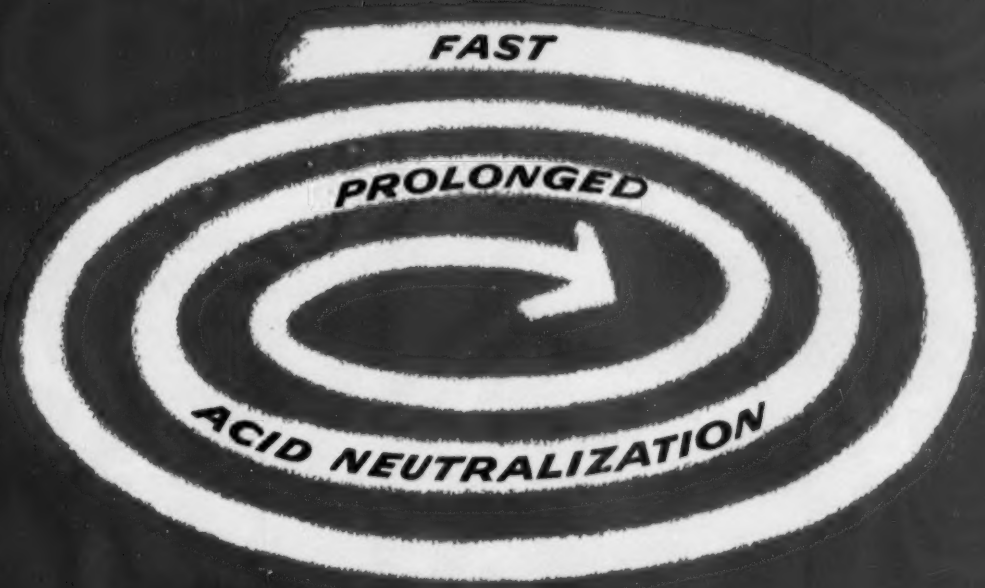

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1. Rossett, N.E., and others: Ann. Int. Med. *36*:98 (Jan.) 1952.
2. Jankelson, I.R.: Am. J. Digest. Dis. *14*:11 (Jan.) 1947.

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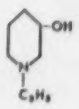

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SUDDEN DEATH DURING PREPARATION FOR ESOPHAGOSCOPY WITH TETRACAINE GARGLE

EDDY D. PALMER, LT. COL., M. C. AND DAVID L. DEUTSCH, LT. COL., M. C. Washington, D. C.

A FATALITY due to preparation for esophagoscopy is being reported, briefly as a matter of record. It is the first instance of death due either to esophagoscopy or gastroscopy with which the authors are personally familiar. It is the fifteenth instance of reaction to local anesthesia that we have experienced. Because this subject has recently been reviewed (1), there will be little discussion at this time. Suffice it to say that anesthetic reaction appears to be the greatest hazard of peroral endoscopy, that local anesthesia adds relatively little to over-all patient comfort during endoscopy, but that most endoscopists believe it to be warranted as a routine because it reduces the danger of the transpharyngeal phase of the instrumentation.

CASE

A 46-year-old white legislator was hospitalized because of dysphagia of nine months' duration. Sudden hematemesis had led to the diagnosis of esophageal varices and the biopsy-proved diagnosis of Laennec's cirrhosis about two years previously at another hospital. There had been no further bleeding, but the patient had been jaundiced continuously for almost two years. The dysphagia had not been severe nor had it been progressive. The patient brought with him films from a recent esophagram, and these seemed to show an annular constricting lesion of the distal portion of the esophagus.

Upon examination, the patient appeared chronically ill, wasted and jaundiced. A hard liver extended 7 cm. below the costal margin in the nipple line during expiration. The spleen descended 5 cm. below the costal margin upon inspiration. There were several spider angiomas and mild ascites. Physical examination was not otherwise remarkable.

Routine and special laboratory studies, chest X-ray, and repeat upper gastrointestinal X-ray examination did not add any important information to that already known about the patient. Esophagoscopic examination was proposed in order to investigate the nature of the constricting esophageal lesion, thought to be carcinoma, and to evaluate the status of the esophageal varices.

Esophagoscopy: The patient gave no history to suggest drug sensitivity. He had had four dental extractions under block anesthesia, without incident. There had been an anesthetic injection into his skin prior to liver biopsy, without incident.

Two and a half hours prior to scheduled esophagoscopy, he was given 0.2 Gm. Nembutal by mouth, and an hour and a half later, 0.0004 Gm. atropine subcutaneously. He arrived at the endoscopy room resting quietly and was seated upon the table. He was questioned again regarding drug sensitivity, and a dental bridge was removed. All of this was routine procedure, no difficulty being anticipated.

From the Gastroenterology Service, Walter Reed Army Hospital, Washington, D. C.

The patient was handed a medicine glass containing about 25 ml. of 1% aqueous tetracaine hydrochloride (without epinephrine) and instructed to take three small gargles, without swallowing, and to expectorate following each. This he did, using all but about 5 ml. of the solution. The tetracaine had been taken from a bottle which had been used for approximately 15 similar patients, without incident, during the previous 8 days.

Immediately after the last gargle, the patient without a sound grasped his chest, gave a little gasp, and immediately seemed to be dead. Four doctors were present, so it was possible to examine him in some detail while emergency measures were carried out. The patient became cyanotic very quickly. The external jugular veins and the superficial veins of the forehead and shoulders were greatly distended. No pulse, heart sound, blood pressure impulse, or diaphragmatic action was ever heard or observed. The body was relaxed and there was no response to any neurologic test. The pupils were in mid-position and did not react to light. Except for the venous engorgement, it was as though the patient had been dead an hour or so, although the observations were made immediately after the patient was seen to be in trouble. It was observed by all present that the incident was remarkably similar to sudden death from coronary occlusion.

Emergency measures were instituted immediately. Artificial respiration with the hand-bellows Field Respirator was begun after a wire air-way had been slipped in place. Sodium amytal, which with the respirator is kept on the shelf at the foot of the endoscopy table, was begun slowly intraveneously, but it soon became clear that barbiturate was not going to be useful. On four occasions the myocardium was directly stimulated by needle puncture and epinephrine deposition, without effect.

At autopsy, severe cirrhosis with esophageal varices and ascites was found. There was no carcinoma of the esophagus. There was considerable coronary sclerosis but no occlusion could be demonstrated. It was the opinion of the pathologists that death had been due to tetracaine sensitivity.

COMMENT

There is no effective way to test for anesthetic sensitivity in the patient who is coming to endoscopy. Patch, intradermal and conjunctival tests are not reliable enough to warrant routine use. Furthermore, a patient to whom local anesthesia proves innocuous at one examination may show sensitivity at the next. Use of a barbiturate prior to local anesthesia appears to be of positive prophylactic value against anesthetic reaction, although there has been some disagreement on this point.

Some experienced clinicians believe that addition of epinephrine to the tetracaine solution is an important

safety measure, because it is said to delay mucosal absorption. The matter of rapidity of absorption seems to be important, although it is admitted that if a true sensitivity is involved, rather than actual pharmacologic poisoning, the amount absorbed should not make so very much difference. We were impressed with the decrease in the frequency of anesthetic reactions which has followed a change in our routine from spray to gargle anesthesia, and explain it by the fact that use of a spray is attended by rapid pulmonary absorption of inspired tetracaine mist. We have not used epinephrine, however, because of lack of faith in its effectiveness in this role and because of worry over epinephrine reactions. The present experience has encouraged us to reconsider our feelings on this matter.

REFERENCE

1. Palmer, E. D.: The risks of peroral endoscopy. U. S. Armed Forces Med. Jour., *5*: 974-994, 1954.

VITAMIN B-12 IN NEURO-METABOLISM (PRELIMINARY CLINICAL REPORT)

M. B. LEVIN, M.D., Baltimore 18, Maryland

THE CHIEF excuse for publication of this report about Vitamin B-12 is to stimulate its more widespread use in sufficient dosage to show its value. Many lives might thereby be saved, or much temporary or permanent relief given to the sick—a good enough reason for its trial. If it would promote or produce remissions in even a limited number of multiple sclerosis or similar types of conditions, where other means failed, it would justify the use. An analysis of failures and subsequent experiments resulted in at least temporary startling successes with this preparation, beyond anything encountered in this field during the past forty years.

My first experience with Vitamin B-12 was in a case of pernicious anemia with spinal cord involvement. 5 cc. crude liver extract (2 units or mcgm per cc.) had been injected intramuscularly three times weekly for 13 years as necessary maintenance dosage. When pure liver-derived Vitamin B-12 (10 mcgm) alone was substituted for liver extract, cord symptoms became so markedly aggravated as to compel the return to crude liver injections. Subsequent addition of the 10 mcgm pure Vitamin B-12 to the full amount of crude liver did not improve the symptoms. When bacterial-derived Vitamin B-12 of higher concentration became available, 60 to 120 mcgm by itself was injected intramuscularly and at other times was added to the crude liver extract, duplicating the previously mentioned unsuccessful results. When 1000 mcgm Vitamin B-12 per cc. became available, 1000 mcgm added to 5 cc. of the liver extract intramuscularly had no effect beyond the previous maintenance dose. When 2000 mcgm B-12 per cc. became available, 5000 mcgm together with 2½ cc. crude liver extract was injected semi-weekly. The 73 year old lady, who previously "rolled all around the room on getting out of bed and often had to be led across street corners," after the second injection of 5000 mcgm inquired: "What dynamite is in that medicine? I do not roll around on getting out of bed. I walk finely and the swelling has gone from my legs and I am better than at any time in the past seven years."

This was repeated in two other pernicious anemia cord complicated cases, in whom the antineuritic Vitamin B-1 (Thiamin) up to 500 mgm orally three times daily previously gave no additional improvement; or, 200 mgm by hypo. three times weekly did not noticeably aid.

Submitted Nov. 17, 1954.

In a lady with multiple sclerosis, whose speech was unintelligible, swallowing very difficult, marked salivation with jaw dropped and difficult dragging walk, a more startling result was encountered. 2000 mcgm Vitamin B-12 was injected intramuscularly daily for two weeks with a halt to the progression of the condition. 3,300 mcgm three times weekly gave slight improvement after one week, so 5000 mcgm B-12 three times weekly was injected. After the second dose, improvement was very marked indeed in speech, swallowing, salivation, walk, etc., and the nocturnal epileptiform seizures, which had been stabilized by drugs for many years preceding the onset of multiple sclerosis, were noticeably lessened in number and intensity, with the same amount of drug. During the past two months 5000 mcgm, once or twice weekly, is sufficient to hold the remission.

Similar results in two more multiple sclerosis cases led to the trial of 5000 mcgm injections two or three times weekly, in cerebral edema and hemorrhage cases with hemiplegia, before and after the use in some patients of cortisone to absorb the clot. While in some the improvement during the elapsed period was more noticeable than the average, it was not nearly as striking as in the multiple sclerosis cases.

One six month old baby, developing amyotonia at six weeks of age and, at eight months weighing 15½ pounds, noticeably improved when 2,500 to 3,000 mcgm Vitamin B-12 was injected intramuscularly three times weekly until now, and further treatment and observation continue.

A 44 year old woman with amyotrophic lateral sclerosis, receiving 5,000 mcgm B-12, three times weekly, for complete paralysis with atrophy of disuse evident in all limbs, torso, neck and speech, after the third dose, was observed kicking during sleep, with markedly improved swallowing, more audible whispering and she noticed that there was a feeling of trying to move the upper limbs. Treatment and observation have also continued here.

Only one other type of cerebral lesion, an encephalomyelitis case, was treated with 5,000 mcgm Vitamin B-12, injected three times weekly, after antibiotics and cortisone for the inflammatory reaction had been used

and I could not definitely decide that the beneficial result could be attributed to one or another of the individual medications. It would be interesting to observe repetitions of this combination of medications in poliomyelitis as well as encephalitis cases.

"Shingles" (radiculitis) in various locations were very responsive to 5,000 mcgm Vitamin B-12, injected three times weekly, either during the active stage when antibiotics were taken, or when pain persisted months after the acute stage. The improvement within seven to ten days was very noticeable in the majority; much more so than when Thiamin alone up to 500 mgm three times daily was taken orally, although a number of "shingles" cases seemed to get adjuvant action when both Thiamin (B-1) and B-12 were taken together.

The large dosage of Vitamin B-12 (5,000 mcgm three times weekly and in some instances 7,500 to 10,000 mcgm+) was successfully employed in cases of neuritis of the cranial nerves as follows:—in retrobulbar optic neuritis with rapid benefit; noticeable improvement of vestibular dizziness (labyrinthian or Meniere's origin); where all other means had previously failed in trifacial neuralgia cases, satisfactory results were obtained; and in Bell's palsy, with fairly rapid improvement.

Peripheral neuritis in various parts of the body, of infectious, drug, traumatic or other origin, where not completely destructive, was noticeably more rapidly and effectively responsive to large dosage of Vitamin B-12 than any other means employed to date.

As stated, an adjuvant action seemed to occur between Vitamins B-12 and B-1 and there is the possibility that some chemical radical, similarly acting or common to both vitamins B-1 and B-12, may be the neuro-metabolic stimulant or alterative. It is possible that when and if isolated it may prove even more effective than either vitamin alone or in combination. However, waiting for this is unnecessary as B-12 to date has proven so much more powerful and effective on all types of nerve tissue than the "anti-neuritic" Vitamin B-1 (Thiamin) itself. Although the marked "high power, high pressure" effects of heroic dosage of Vitamin B-12 on neural tissue have been clinically observed during the past year, the time and opportunity for animal experimentation, to determine the exact location in nerve tissue of the marked neuro-metabolic effects, has been lacking. Was it in the neuro-keratin (or other insulating materials); or, did it occur in the neuro-lipoprotein tissues (the transmitting wires themselves), a matter which will have to be decided by further animal experiments on live as well as dead, or fixed, neuro-coagulated fibers?

In adults and the few children given B-12 *by mouth*, it has failed completely to give results comparable to the intramuscularly injected large dosage. The possibility does remain to try 5,000 mcgm tablets, plain or enteric coated, two or three times daily (if available and not prohibitive in price), to see if this could substitute comparable effects.

Often, when the large intramuscular dosage was administered, any unused or excessive quantity beyond that required by the body was found in the urine within one or two hours following the injection. To date it has not appeared in the urine of the infant with amyotonia weighing 15½ pounds and getting 2,500 to 3,000 mcgm B-12 intramuscularly three times weekly.

In a few instances patients receiving 7,500 to 10,000 mcgm B-12 before breakfast had the general metabolism sufficiently stimulated to give attacks resembling mild insulin attacks; and, this decided that all large dosage B-12 be given at least one hour after food was taken, or in the evening.

In two patients having paroxysmal tachycardia with noticeable repeated irritation of the cardiac sympathetic nerves, in addition to the usual measures employed without success, to reduce the frequency of attacks, Vitamin B-12 in large dosage seemed to lengthen the intervals and in most instances, the severity of the attacks.

The neurologic effect of Vitamin B-12 in large dosage was outstanding, in addition to its having a good general "tonic" effect, whether the "run-down" condition occurred with or without anemia subsequent to infection or other usual condition producing this. To date I have not definitely decided that even this large dose of Vitamin B-12 can entirely replace the use of liver in pernicious anemia, but it is certainly a great aid in treating its neurologic complications in addition to liver extract.

SUMMARY AND CONCLUSIONS

1. Vitamin B-12 injected intramuscularly in large quantities and in maintenance dosage is the most active stimulant to neuro-metabolism; and, alterative, to the nervous system, encountered to date.

2. The effect was noticeable on all parts of the nervous system from the central cerebral to terminal neuritic, including the sympathetic system and posterior spinal roots.

3. It has been ineffective orally in adults and children in similar dosage.

4. Between 5,000 and 10,000+ mcgm injected intramuscularly, two or three times weekly was necessary for effective dosage in the various types of neurological cases.

5. Some neurological conditions, up to now considered "irreversible," if not beyond a certain stage, may be "reversible" under full Vitamin B-12 attack.

6. Animal experiments may indicate the exact location in nerve tissue of the marked neuro-metabolic effects of sufficient dosage Vitamin B-12 injected intramuscularly.

218 E. University Parkway.

EFFECTS OF PORTAL VENOUS AND HEPATIC ARTERIAL OCCLUSION ON THE NORMAL AND CIRRHOTIC LIVER

JACOB K. BERMAN, M.D. AND HUBERT E. JUDY, M.D., Indianapolis, Indiana

IN PREVIOUS publications we have indicated the possible types of circulation which occur in the normal and cirrhotic liver (2). Our hypotheses based on experimental and clinical observations indicated that the shrunken atrophic cirrhotic liver gradually narrows the portal venous-hepatic arterial sinusoidal juncture and that the competition of pressure between the two is increased due to more intimate communications thereby increasing portal venous pressure so that the portal vein may continue to contribute its share to the blood supply of the liver. The rationale for ligation of the hepatic artery was also described in many previous publications (3). However, we found that ligation of the hepatic artery close to its origin does not completely interrupt the hepatic arterial blood supply whereas ligation close to the liver usually does. But the latter procedure is followed by death in all experimental animals and is dangerous in man. Therefore, we believe that the hepatic artery should be occluded gradually, allowing for hepatic acclimatization (3,7). This is rational because complete interdiction of the hepatic arterial inflow is followed in the experimental animal by greater amelioration of ascites than is ligation close to the celiac axis. Moreover, the huge cavernous hemangioma of the splanchnic area may be more effectively controlled by simultaneous ligation of the left gastric and splenic arteries.

In advanced atrophic cirrhosis an angiomatous transformation also takes place within the liver creating in effect a comparatively greater blood supply especially in the portal venous and hepatic arterial radicles (15). However, the hepatic venous branches are reduced in number and the pressure within them is greatly increased equalling that in the sinusoids and portal venules.

Ligation of the portal vein in experimental animals and in man is not followed by typical ascites. However, a gradual occlusion of the hepatic veins or the inferior vena cava just above the diaphragm produces a prodigious amount of ascites (5). Therefore, it would seem that the obstructing factors are in or around the hepatic venous tributaries within the liver rather than at the hepatic arterial-portal venous sinusoidal juncture. We believe that occlusion of the hepatic artery close to the liver by a slow or graded method would reduce the inflow from this branch of the hepatic circulation and induce the formation of collaterals (3), thereby increasing arterial frictional resistance. The effect of the increased surface upon resistance to the flow of blood would be great because frictional resistance is proportional to the extent of the inner surfaces of narrow vessels, not only because of more resistance offered by the many small walls but also because of the friction between the molecules and the cells of the blood stream (internal friction). This is a fundamental physical principle in viscid fluids and is called the *force of viscosity*. Thus the corpuscles nearest the wall are stationary whereas those in the actual stream move swiftly. In the comparatively large hepatic artery rolling and internal friction will be less than in the many collaterals we induce by gradual hepatic arterial interruption. In this way we hope to cut down on the high arterial pressure and supply the oxygenated blood through many small vessels which, because of the increased frictional resistance, would cut down on the competition of flow between the hepatic and portal venous pressures. The net result of this should be a lowering of the hepatic venous pressure, and as a result of this there should be an amelioration of the two most lethal complications, namely, ascites and esophageal hemorrhage. Some observers (9) have found that a change in hepatic venous pressure occurs in cirrhotic dogs. However, we do not believe that the complete counterpart of atrophic cirrhosis as observed in man can be reproduced in experimental animals.

From the Departments of Surgery, Indianapolis General Hospital and Indiana University School of Medicine. Aided by a grant from the Charles J. Wolf Foundation for Medical Research.

Submitted Nov. 29, 1954.

PHYSICAL PRINCIPLES INVOLVED IN THE RELATIVE INCREASE IN ARTERIAL CIRCULATION IN THE CIRRHOTIC LIVER

Some of the physical factors which we had previously not included in our discussions should be brought out to explain the angiomatous transformation which takes place in the liver and to explain our original hypothesis that the obstruction is pre-sinusoidal and perhaps to a lesser extent in the hepatic venules due to fibrosis. The increase in hepatic venous pressure is explained in part by the Bernoulli principle (12). In general, it may be stated that when a ligature or a constriction is placed in the course of a blood vessel that collaterals will form as depicted in our previous publications (2,3,4). This is especially true in arteries and because of the juncture of portal vein and hepatic artery it would apply to the sinusoids. This is predicated on the hypothesis that there is a conservation of energy in fluid flow, and that the high kinetic energy on the proximal side of the constriction is converted into high potential energy or lateral pressure resulting in lateral deflection, the formation of eddies, and possible reversal of flow producing various pressures in an elastic wall and capable of producing structural fatigue with dilatation. These pressures may be measured by the Venturi meter (6). This is the explanation for poststenotic aneurysmal dilatation and this same phenomenon may occur to a lesser extent in the portal vein within the liver. Furthermore on the proximal side of the constriction the hypertrophy of the vessel and the collaterals decrease the liability of dilatation distally, although it is known that the hepatic artery is enlarged to some extent. Therefore poststenotic dilatation will

be decreased in direct proportion to the formation of collaterals.

Motion of fluids or hydrodynamics may be described under the headings of streamlined flow and turbulent movement. In streamline motion the filaments move in definite paths and the resistance to flow is due purely to the sheer or adjacent layers and is directly proportional to the viscosity and to the velocity. In turbulent motion the water or liquid moves in an eddying mass and the motion at a given point varies in an irregular manner from instant to instant. The resistance is only to a slight degree dependent on the viscosity and is proportional to the nth power of the velocity where n is approximately equal to two. At very low velocities then the motion is usually streamlined but as the velocity is increased the motion breaks down and becomes turbulent. For any particular case there is some particular velocity at which the change over from one type of motion to the other takes place and this is known as the *critical velocity*. Several conditions combine to determine whether the motion of a fluid shall be streamlined or turbulent. Osborn Reynolds' laws indicate that the conditions tending to the maintenance of streamline motion are: 1) an increase in the viscosity of the fluid; 2) converging solid boundaries; 3) free, that is exposed to the air surfaces; 4) curvature of the path with the greatest velocity at the outside of the curve, and 5) a reduced density of the fluid. The reverse of these conditions tends to produce turbulence. Where two streams of fluid are moving with different velocities the common surface of separation is in a very unstable condition. This is the situation at the portal venous hepatic arterial juncture with the sinusoids. Generally speaking wherever the velocity of flow is increasing and the pressure is diminishing, as where lines of flow are converging, there is an overwhelming tendency to stability of flow. In a tube with converging boundaries this effect is sufficiently great to overcome the tendency to turbulent motion to which all solid boundaries of whatever form give rise, and the motion in such tubes is stable for high velocities. On the other hand, as in atrophic cirrhosis of the liver, the tendency to eddy formation is very great wherever the lines of flow are diverging and the velocity is diminishing in the direction of flow. This is easily shown by the Reynolds experiment. A water tank with an outlet valve is filled with water and a small amount of anilin dye solution is introduced at the entrance to the tube through a fine tube supplied from a separate receptacle. As the velocity of flow is gradually increased by opening the outlet valve the color band becomes more attenuated still retaining its definition, until at a certain velocity eddies begin to form, at first intermittently near the outlet of the tube. The apparent lesser tendency to eddy formation near the inlet end of the tube is due to the stabilizing influence of the convergent mouthpiece.

The Bernoulli principle applies whether one or many channels are stenosed. Dilatation of the poststenotic areas will occur in proportion to the frictional resistance and the transformation of kinetic into potential energies. The exact site of these dilatations is not always easily ascertained, especially where many smaller vessels are involved. This is particularly true in the cirrhotic liver because of the disproportion of pressures in the portal vein (15-25 mm. Hg.) and the hepatic artery (120-140 mm. Hg.). However, the dilatation of the outlet of the two streams which converge to empty into the hepatic vein must be at some small distance distal to the portal-venous-hepatic arterial-sinusoidal juncture which is at a point beyond the narrowing and distortion which occurs around the central and sublobular veins. Thus, velocity (kinetic energy) is decreased and lateral pressure (potential energy) is increased in the hepatic venous system within the liver. This entire picture is complicated by the fact that there are veno-venous collaterals which form between the portal vein and hepatic vein and arterio-venous communications between the hepatic artery and portal vein and also the hepatic artery and hepatic vein. This produces, in effect, a huge cavernous hemangioma as described in one of our papers (7). The great increase in hepatic venous pressure is not apparent in the normal liver no matter what the momentary inflow variations may be. This is due to the great elasticity of the normal organ and the balance which takes place between inflow and outflow vessels.

HEPATIC VENOUS DILATATION

Since the liver has a peculiar blood supply a constriction placed in the portal hepatic venous juncture would have, to a lesser extent, the same effects as those on the arterial side because the flow is onward and is not interrupted by a difference in direction as in an extremity (2). The sinusoids being the continuation of the portal vein and hepatic artery, there would then follow also a poststenotic dilatation on the hepatic venous side due to the Bernoulli principle as previously discussed. If, however, we take into consideration the added increase in pressure on the proximal side of this constriction due to the inflow of hepatic arterial blood it is evident that the principle becomes even more apparent, lending credence to the hypothesis that hepatic venous pressure is increased within the liver and that this may be a contributing factor in causing the lethal complications of atrophic cirrhosis. Dilatation of the hepatic venous radicles is not so apparent in the cirrhotic liver due to perivenous fibrosis.

FEASIBILITY OF PORTAL VENOUS LIGATION

It has been shown experimentally and clinically that sudden interruption of the portal vein can be accomplished in monkeys and humans with survival in about 70 to 80% of the cases. It has also been shown by end-to-side porta-caval shunting that the liver can function without portal venous inflow, and that it can regenerate to a limited extent. Child has also shown that the liver will regenerate more completely after the vena cava has been anastomosed to the proximal side of the portal vein than after occlusion of the portal vein and porta-caval shunt. Sudden ligation of the portal vein is practically always fatal in the dog if no provision is made for portacaval outflow. However, this is not the case in the Macaca mulatta monkey and in man. Child has reported seven patients who have survived sudden and complete interruption of their portal circulation. He believes that the mortality from ligation alone is about 10 to 20% (8a). It should, however, be possible to avoid any immediate deaths with permanent ligatures by temporarily occluding the

vein and observing the systemic blood pressure. Should the blood pressure fail to return to preocclusion levels within 20 to 30 minutes after occlusion the patient will probably not tolerate the procedure. The "trial occlusion" is necessary as a preliminary step in a radical resection of the portal vein by the two stage operation. In most cases the deaths which occurred were due to thrombosis of the portal vein and this, we have observed in all dogs following portal ligation. Many experimenters have considered the possibility of treating cirrhosis of the liver by venous occlusion (8b) and Madden ligated the superior mesenteric vein in an effort to relieve the liver of some of the burden of its blood flow (16). The patient promptly developed extensive splanchnic infarction and died. We have observed one patient with an advanced atrophic cirrhosis in which the surgeon deliberately ligated the portal vein to accomplish the same purpose. This patient died in shock within a few hours after surgery. Thus the portal vein may be occluded suddenly, but the effects upon the extrahepatic portal bed might lead to a catastrophe although the effects upon the liver itself may not be devastating because of the influx of oxygenated blood from the hepatic artery. However, the ability of the liver to regenerate in the absence of either portal venous or systemic venous blood is markedly curtailed. Therefore ligation of the portal vein as a therapeutic measure in atrophic cirrhosis is unwarranted because of the risk involved and the fact that pressures in the hepatic veins within the liver are not permanently reduced due to the great influx of hepatic arterial blood at a pressure of 120 mm. of Hg. without any competition from the portal venous side of the juncture.

EFFECTS OF HEPATIC ARTERIAL AND PORTAL VENOUS OCCLUSION

Ligations of the portal vein and the hepatic artery with or without portacaval shunts are uniformly fatal in dogs even when protected by antibiotics. Death occurs within a few hours from mesenteric thrombosis and shock. The abdominal cavity is filled with a bloody serosanguinous exudate and the intestines are dark and undergoing early necrosis.

The normal liver will tolerate hepatic arterial interruption if the dogs are prepared with penicillin and streptomycin as originally advised by Markowitz (17) but it will not tolerate ligations close to the liver. However, in sharp contrast to the dog the Macaca mulatta monkey does not harbor the Welch bacillus type of pathogenic organisms and therefore resection of the hepatic arterial tree together with all its twigs is not fatal. Complete interruption of the hepatic arterial supply close to the liver in man results in massive infarction and death generally without any evidence of intrahepatic bacterial proliferation. Only when some measure of hepatic arterial inflow is preserved can the liver survive and thus ligation of the hepatic artery on the liver side of the gastroduodenal vessels is usually fatal unless, as in the case of advanced atrophic cirrhosis there has been time for vascular adjustment. Neither the dog nor the monkey survives occlusion of both the hepatic artery and portal vein simultaneously even though portacaval shunts are made. Child (8c) reported a case in which he resected the portal vein and inadvertently placed a ligature tightly about an aberrant branch of the right hepatic artery during an end block resection of the head of the pancreas for advanced carcinoma. At autopsy the left hepatic territory was normal but the right was the site of massive ischemic infarction. The patient expired five days after operation with a high fever and anuria. Rappaport (19, 20) and Popper (18) and their associates interrupted the blood supply to the liver in stages "to see the result when the liver apparently survives upon what it borrows from its neighbors" (20). These animals presented practically all the features of non-lethal hepatic decompensation. In some animals widespread edema appeared which could be controlled by liberal administration of 50% glucose solution. Five dogs subjected to this technique died after 31 to 96 hours in coma. Five animals were in coma from 3 to 7 days and then recovered. The success of the experiments depended upon the care with which the stages were spaced. Rappaport expressed the conviction that the clinical picture appearing in these animals had many features which were comparable with hepatic ischemia. Thus we may conclude that sudden interruption of both hepatic and portal venous inflow is fatal to both experimental animal and man. In the experimental animals the hepatic inflow may be gradually occluded with survival of about 30% of the animals but they develop symptoms of a hepatic insufficiency which is ultimately fatal.

GRADUAL OCCLUSION OF THE HEPATIC ARTERY AND OF THE PORTAL VEIN IN THE EXPERIMENTAL ANIMAL AND IN MAN

Some of the lethal complications of advanced atrophic cirrhosis are ameliorated by gradual hepatic arterial occlusions close to the liver. We have done this in the experimental animal and in man by the use of a ¼" cotton tape band on which dicetyl phosphate had been dusted and also by the use of Ameroid* (3). This material is a casein derivative which has the property of expanding in the presence of moisture. When placed in an inexpansile stainless steel button with a small slit down the center it may be slipped over the artery without difficulty (see Figure 1). The hepatic artery or arteries are completely occluded after 3 to 6 weeks in the experimental animal and at a second operation the

Fig. 1.—Photograph of Ameroid button used in occluding the hepatic artery. This is lined with Ameroid, the lumen of which is narrowest at its midpoint so that thrombosis will not occur on its proximal end. The coating is made of stainless steel. It is apparently well tolerated by the tissues with minimal reaction.

***Produced by American Plastics Company. We are indebted to Doctor Robert Shipley for acquainting us with this material.**

arteries may be excised close to the liver with no untoward effects. In fact, we have placed a larger button of this same type around the abdominal and thoracic aorta in dogs and at the end of eight weeks these vessels were occluded without apparent deleterious effects. A more detailed description of our experimental work will be published at a later date** (7). The same procedure was done with the portal vein. Here the button had to be constructed so that the occlusion was extremely gradual. The animals survived this procedure also without ascites or bleeding from the gastrointestinal tract. In a third group of dogs the hepatic artery and then the portal vein was slowly occluded by this method. Such animals develop a syndrome in which there is intolerance to meat and gradual hepatic incompetency. However, we are aware of one case in which the hepatic artery was ligated close to the celiac axis, later a portacaval shunt was done successfully. The patient had bleeding esophageal varices although at the second operation the portal pressure was close to zero. A follow-up has not been obtained on this and one other patient treated in a similar manner. These cases will be reported in the near future (1). Simultaneous application of these bands to the portal vein and hepatic artery in dogs showed the same effect as alternate occlusions and 30% of the animals survived. Lastly, in one dog the hepatic artery and portal vein were occluded with an ameroid button and at the same time the splenic and left gastric arteries were tied. This animal also survived the procedure for seven days dying of hepatic insufficiency. We realize that the number of animals have been too few to draw any valid conclusions as to what effect these procedures may ultimately have. We have not tried portal occlusion in man although gradual interdiction of the hepatic arterial inflow has been successfully used in patients with advanced atrophic cirrhosis with ascites and bleeding varices.

SUMMARY

Lethal complications of cirrhosis of the liver are probably related to an increase in hepatic venous pressure. This does not occur in the hepatic vein as it leaves the liver. It probably occurs in the sinusoids or immediately distal to the sinusoids in the sub-lobular vein because the pressures in these structures are comparable to the pressures in the portal vein.

Simultaneous ligation of the hepatic artery and portal vein is fatal in the experimental animal as is also simultaneous ligation of the hepatic artery and production of a porta-caval shunt.

The production of an ischemic liver in dogs by gradual occlusion of the hepatic artery and portal vein will result in phenomena which occur in advanced atrophic cirrhosis but there is apparently no increase in intrahepatic venous pressure with ascites and bleeding varices, although dogs do not develop esophageal varices under any condition.

Ligation of the portal vein causes a fall in hepatic venous pressure. Pressure in the portal vein is increased on ligation and it is also increased in cirrhosis. However, the pressure in the portal vein gradually falls with the development of collaterals should the animal survive. We have not attempted gradual occlusion of the portal vein in man. However, it has been successfully carried out in dogs.

Ligation of the portal vein as a therapeutic measure in advanced cirrhosis would accomplish very little and would simply augment the arterial inflow into the sinusoids probably increasing the pressures to a greater degree. The same may be said of an Eck fistula.

Certainly, gradual occlusions of both hepatic artery and portal vein which would develop complete devascularization making the liver depend entirely upon its collateral circulation with low pressures would compromise the diseased organ even more.

The cause of the increase in pressure in the hepatic vein radicles within the liver is not definitely known (10,11). Kinsely and his associates (13,14a & b) found that under some conditions the tips of the hepatic artery open up pouring arterial blood directly into the sinusoids and pouring "torrents" of blood through arterio-portal anastomoses into the portal vein which then conducts pure arterial blood into all sinusoids. Some of the mechanisms involved in the altered circulation in advanced atrophic cirrhosis lead to the conclusion that the phenomena associated with post-stenotic dilatation occur in the sub-lobular veins.

A gradual method of occlusion of the hepatic artery is safe and is indicated in advanced atrophic cirrhosis because it removes the greatest contributor to inflow pressures and thereby decreases post-stenotic pressures in the hepatic venous tributaries.

**Ameroid buttons are used in the following dimensions:

The external diameter of the plastic is two times the luminal diameter;

The slot in the button is one-third of the luminal diameter;

The length of the button is variable depending on the diameter of the button and varies from .75 centimeter to 2.5 centimeters; usually it is 2 times the external diameter.

The metal used to encase the Ameroid is surgical stainless steel; This metal is spun on the Ameroid.

The luminal diameter of the Ameroid should be very slightly larger than the external diameter of the vessel on which it is used—so that the button fits snugly on the vessel but does not constrict it.

The rate of arterial or venous constriction depends on the diameter of the vessel—for instance: the renal artery of a dog will be occluded in a period of three to four weeks while the abdominal aorta requires six to eight weeks for complete occlusion.

The thickness of the metal used to encase the Ameroid has varied from .75 to 1.5 mm. The critical thickness of stainless steel which will prevent the Ameroid from expanding outward rather than inward has not been determined.

No instances of thrombosis have occurred in use of these buttons.

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PRACTICAL AMBULATORY THERAPY OF FUNCTIONAL CONSTIPATION

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"CONSTIPATION" is a frequent primary or secondary complaint among patients of all ages from all social strata. Indeed, Bargen (1) has said that "constipation is probably the most common of all physical complaints." It is incumbent on the physician to determine what is meant by the term. A patient may wish to indicate that his stools are firm and difficult to pass, but that he has a daily evacuation. Another patient may have spontaneous bowel movements every two to ten or more days, with variable degrees of distress and difficulty. Because of poor toilet training in childhood or prolonged failure to respond to the natural urge for a bowel movement, the more severely affected patient has no spontaneous bowel movements but must utilize laxatives or enemas; over a period of years this routine will lead to diminished sensitiveness of the rectal reflex. Modern therapy of constipation aims for ease, but not necessarily for regularity, of defecation.

After a study of the gastrointestinal tract in individuals over sixty years of age (2), the author undertook a further study of constipation among young enlisted men in the United States Army, feeling that this would offer an interesting comparison. This study has been continued during subsequent civilian practice, in an effort to evaluate the complaint of constipation among patients of all ages and to observe the effects of a practical ambulatory plan of therapy for these patients. It has been my purpose to enable these patients to have normal bowel habits without the use of harsh laxatives and cathartics and to wean them away from these disagreeable habits if they pre-existed, thereby preventing resultant irritation of the colonic and rectal mucous membrane, bowel atony, fissures and possibly hemorrhoids.

The milder constipations evidenced by a tendency to hard, firm stools may often be relieved by inducing hydrocholeresis with dehydrocholic acid. (Decholin® —Ames.) Bile is a normal laxative for the intestinal tract, and hydrocholeretics appear superior to choleretics and cholagogues, because hydrocholeretics are more likely to protect against colonic dehydration which might cause hard stools. Because more stubborn cases of constipation are usually related to "left-sided" constipation due to inhibition of the sacro-pelvic nerves, over which is carried the evacuation reflex, it has been helpful in the past to administer neostigmine (Prostig-

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min®—Roche), to stimulate the motility in the left half of the colon. This has been equally effective orally as parenterally. More recently the oral form of the urethane of beta-methylcholine (Urecholine®—Merck) has been available, and this, too, was tried as ambulatory therapy in a few patients.

MATERIAL AND METHODS

The 115 patients in this study fall within three groups:

1. *"The Army Group"*—Thirty-five young male soldiers between the ages of 17 and 26 complaining of constipation were seen among one thousand consecutive patients referred to the out-patient medical clinic of an army hospital. Some had been referred because of constipation, but the majority had been sent to the clinic with various cardiac, pulmonary, or other gastro-intestinal complaints. Each of these men was the subject of a detailed gastro-intestinal and general systemic history, complete physical examination, gall bladder, upper gastro-intestinal, and barium enema X-ray series, stool examinations for blood and parasites, hemogram, basal metabolic rate and urinalysis. Particular attention was paid toward ruling out carcinoma of the lower bowel, and proctosigmoidoscopy was done whenever indicated. Each patient kept a record of bowel movements during the course of the laboratory examinations and again after treatment had been begun. Because of transfers away from the army post, twenty of the men were not able to complete the study and thus were excluded, leaving fifteen for prolonged observation. Nevertheless, the 3.5% incidence of constipation among these young men is a very significant figure, since this is a much smaller incidence than Ivy's (3) observation of 31% constipation among 1,082 college students.

2. *"The Civilian Group"*—The second group is comprised of forty-one private patients between the ages of 18 and 68 who have had a primary or incidental complaint of constipation. Each patient has had a complete history and physical examination and laboratory work as indicated. All had complete gastrointestinal X-ray studies.

3. *"The Aged Group"*—The third group consists of fifty-nine patients over the age of 60 who have been included in a previous report (2). These patients comprised 44.4% of the total group. They, too, were studied in detail before and during treatment. Where indicated some of the data from the previous report have been included here for comparison.

Following clinical and laboratory evaluation, the patients were given suitable dietary and medical management to control the general clinical picture. In addition they were given some form of medication to aid the initiation of proper bowel habit.

The patients were most often started initially on dehydrocholic acid (Decholin®) to determine the effect of a simple, available, inexpensive, and physiologic stimulant to evacuation. Following adequate trial with various dosage schedules, the patients who did not respond were given one of the parasympathomimetic drugs, Urecholine® or Prostigmin®, orally or parenterally.*

RESULTS

The entire series of three groups is distributed according to age and sex as shown in Table 1.

The army group is admittedly a selected one, since, with the exception of two men (one with hematuria and one with cellulitis), all of the fifteen who were ultimately included in this study had the primary complaint of constipation. Because their constipation was of such a degree as to preclude effective duty, five of the fifteen patients were followed initially in the hospital. Six men in this group stated they had occasional blood on the toilet tissue after passing a hard stool.

Among the civilian group only three had a primary complaint of constipation. Eight complained of fatigue and eight of obesity. Eleven had gastrointestinal complaints such as nausea, belching, abdominal pain, heartburn, or previously diagnosed duodenal ulcer. Seventeen had observed blood on toilet tissue after difficult movements, and one housewife said she had occasionally noticed blood in the toilet bowl. Nine had symptoms referable to the cardiovascular system, and the remainder had arthritic, dermatologic, or gynecologic complaints. One patient was obese, pregnant, and constipated. The relative degree of constipation in the three groups is shown in Table 2.

Physical examination in all three groups was essentially non-contributory in relation to the constipation in these patients, except in one patient who had a rectal stricture following previous hemorrhoidectomy. Vague abdominal tenderness, palpation of various portions of colon filled with firm feces, and (in thirteen patients) clinical and proctoscopic evidence of internal and/or external hemorrhoids were observed. Twelve additional proctoscopies were normal.

Hemograms were done in each case. No abnormali-

*Decholin and Decholin with Belladonna were generously supplied by Ames Company, Inc., Elkhart, Indiana. Urecholine was generously supplied by Merck & Co., Inc., Rahway, N. J. Prostigmin was supplied in part by Hoffmann-LaRoche, Inc., Nutley, N. J.

TABLE 1

DISTRIBUTION OF PATIENTS ACCORDING TO AGE AND SEX

Age	17 - 30		31 - 40		41 - 50		51 - 60		Over 61		Total	
	M	F	M	F	M	F	M	F	M	F	M	F
Army	15	0	0	0	0	0	0	0	0	0	15	–
Civilian	1	7	1	8	5	4	1	7	2	5	10	31
Aged	0	0	0	0	0	0	0	0	29	30	29	30
Total	16	7	1	8	5	4	1	7	31	35	54	61

TABLE 2

SUMMARY OF PATIENTS' BOWEL HABITS

Frequency of Bowel Movements

	Intermittent	Daily Hard Stool	1 - 3 days	4 - 6 days	Weekly	7 - 14 days	Only with Laxatives	Only with Enemas
Army	–	–	4	3	2	2	3	1
Civilian	–	1	22	7	2	1	7	1
Aged	10	–	23	13	4	1	5	3

tics found were related to the constipation. Stool examinations were negative for occult blood except in three patients, and these were negative after institution of corrective therapy and subsidence of active bleeding from hemorrhoids; urinalyses, blood chemistries and electrocardiographic findings were not considered to be related to constipation in any patient.

Table 3 indicates that the basal metabolic rate was most often within normal range in the three groups of patients. There was no correlation between frequency of bowel movements and high or low metabolic rates; that is, the patients with higher rates often had less frequent evacuation, while some of those with lower rates had more frequent movements.

These conclusions agree with the previous findings (2). Although constipation is a frequent accompaniment of lowered metabolic rates (4) thyroid, in sufficient doses to bring the metabolism to within normal limits, was ineffective in producing improvement in bowel evacuation in the seventeen patients with low rates in this series; additional medication was necessary.

RADIOLOGICAL FINDINGS

Results in the aged group have been reported in detail previously, and will be mentioned here only for purposes of comparison. In the army group gall bladder visualization and emptying were normal in all fifteen patients. In the civilian group four patients had good concentration but poor emptying, one had poor concentration but good contraction, one had a stone with poor concentration and no contraction, and thirty-five were normal. Thus, in the entire present series of 115 examinations 82 showed normal gall bladders according to the roentgenological findings. Four patients had calculi, and twenty-nine had subnormal cholecystic function—either poor concentration or poor emptying.

Numerous investigations into the relationship of biliary tract function and gastrointestinal motility have been made in animals (5) and in man (6). It is the consensus (7) that improving biliary function and relieving constipation have a mutually beneficial effect.

Examinations of the stomach and duodenum in the army series were within normal limits. In the civilian group four had hypertrophic gastric mucosal patterns, two had gastroptosis and one had only one-third of the stomach remaining after gastric resection for duodenal ulcer. One patient had an active duodenal ulcer, one had duodenitis, and another had a scarred duodenal bulb following a previous ulcer. The remainder were normal. All of these patients had normal gastric emptying time. Examination of the small intestine was normal in all cases.

Table 4 shows the variation in small intestine motility in the three groups. It will be observed that the great majority of patients in each group as well as in the total series fall within the limits of normal motility. None of the patients newly described in this study had a hypomotility. As previously suggested (2), small intestinal motility is probably unrelated to constipation.

Barium enema examinations revealed normal colons in twelve of the army cases, distended atonic descending colons in two, and one redundant sigmoid in this group. In the civilian group there were thirty-four normal colons, one markedly redundant colon, one redundant sigmoid, and one markedly dilated rectal ampulla. Rectosigmoid diverticula were seen in one of the civilian patients.

The patients included in the three groups of this study may be considered to have a functional constipation because of lack of contributory organic findings, inconclusiveness and inconsistency of the laboratory data, and the response of these patients to a relatively simple plan of therapeutic management.

TABLE 3

DISTRIBUTION OF BASAL METABOLIC RATES

	+11% to +19%		+10% to −10%		−11% to −19%	
	Male	Female	Male	Female	Male	Female
Army	3	0	11	0	1	0
Civilian	0	0	3	17	0	1
Aged	3	3	9	18	9	6
Total	6	3	23	35	10	7

TABLE 4

MOTILITY OF SMALL INTESTINE

	Hypermotility (less than 2 hrs.)	Normal (2 - 5 hrs.)	Hypomotility (more than 5 hrs.)
Army	–	15	–
Civilian	26	15	–
Aged	8	47	4
Total	34	77	4

THERAPY

As a basic form of therapy the patients were instructed to eat diets with high-residue foods and liberal fluid intake, similar to management previously outlined (2,8). They were encouraged to establish a bowel habit at a convenient time of day when they would be more relaxed. Exercise was also encouraged, although this was not a problem among the army group. However, this form of management, without medication, had previously not proven to be sufficiently effective to correct the constipation of any of the patients included in this study.

Many of the army men who had a family history of gastrointestinal disorders—and especially constipation—were referred for psychiatric evaluation. All of these men fell within the "passive—aggressive" classification. Among the other patients family histories were thoroughly investigated, and often a history of parental constipation and/or parental insistence on daily bowel evacuation was elicited.

Because the environmental etiology of constipation has long been appreciated (9), the relationship of each patient's emotional tensions to his functional constipation was pointed out. The patient was given reassurance, he was told that his symptoms were real, and that his reaction to stress had produced only transitory bowel changes.

Medical therapy was given the patients in accordance with their primary complaints, whether gastrointestinal or otherwise. For their functional gastrointestinal symptoms they were given a mild sedative in the form of small doses of phenobarbital (.015 to .03 Gm.) four times daily at mealtime and bedtime. One of the parasympatholytic drugs was given to relieve spasm and, if present, small bowel hypermotility.

Initially atropine sulfate was given to each patient, in doses of from 0.4 to 0.6 mg. When it later became available a tablet containing dehydrocholic acid with belladonna (Decholin® with Belladonna—Ames) was administered. Supplementary vitamins were prescribed when indicated.

Initially all of the patients in the entire series were given dehydrocholic acid, a hydrocholeretic, to increase the flow of the physiologic laxative, bile. This is much to be preferred to the administration of mineral oil, which is only a lubricant, depresses absorption of the fat soluble vitamins and of essential fatty acids, and has no effect on distal colon stasis (10); to one of the hydrophilic colloids, which, although effective according to some reports (1,10), can produce a perforation of the bowel (11,12); and to prolonged use of enemas and harsh laxatives, which may lead to colitis (13).

One of the functions of bile is to augment intestinal motility (14); and the oxidized conjugated bile salts given orally are the best hydrocholeretics (15); that is, they are an additive therapy to produce a more copious flow of thin bile. Commercially available dehydrocholic acid (as Decholin®—Ames) is chemically pure 3,7,12 triketocholanic acid (15a). For several years it has had a popular place among physiologic laxatives (2,15,16). Doses of 0.25 Gm. (one tablet) were given two or three times daily with or after meals, as indicated by the frequency of bowel movements and degree of hardness of the stools. There is a wide difference in individual response to dehydrocholic acid—some patients having frequent loose stools while taking one or two tablets daily, others requiring up to six or eight tablets daily, and the remainder showing no response to larger doses.

Table 5 shows the improvement observed during the initial dose of two to four Decholin tablets daily. Those in the group showing marked improvement (80.9%) had softer stools every day or two, without the necessity for laxatives or enemas. The majority of patients with marked improvement (whether after initial or increased dosage) were able to decrease the dosage of dehydrocholic acid to one or two tablets daily within a short time, with subsequent maintenance of satisfactory evacuation. A few patients had established normal

TABLE 5

RELATIVE IMPROVEMENT OF EVACUATION DURING INITIAL THERAPY WITH DEHYDROCHOLIC ACID

	Total	Marked		Moderate		None	
		Number	%	Number	%	Number	%
Army	15	8	53.3	5	33.3	2	13.4
Civilian	41	36	87.8	4	9.8	1	2.4
Aged	59	49	83.0	10	17.0	0	–
Total	115	93	80.9	19	16.5	3	2.6

bowel habits so successfully that they could discontinue the drug altogether.

Those with moderate improvement (16.5%) required less frequent utilization of enemas and/or laxatives, but these patients did not have satisfactorily frequent or complete evacuations. In this group of three patients, 0.5 Gm. dehydrocholic acid was given three times daily as an initial dosage, which was followed by daily movements. Three army patients and one civilian patient with only moderate improvement were given in addition Prostigmin® or Urecholine® with excellent results. (These will be discussed later.) A few patients found it necessary to take an occasional enema over the initial one or two weeks of therapy, but these were discontinued with the onset of desired results.

Two army patients and one civilian (2.6%) showed absolutely no effect after large doses of dehydrocholic acid (up to three tablets three times daily). These patients were later given Prostigmin® or Urecholine®, with only moderate improvement in the civilian patient and none in the army men.

One army and five civilian patients complained of frequent watery stools after the initial dose of three Decholin tablets daily. This was the only side effect observed, and was minor, because it subsided completely with discontinuance of Decholin for one or two days, and did not reappear when a smaller dose was reinstituted. None of the patients complained of abdominal cramping, and no tolerance to the effective dose developed during follow-up periods as long as four years in some patients.

None of the patients who improved with dehydrocholic acid therapy had further rectal bleeding, because the stools were softened. Rechecks of the stools which had been positive for occult blood showed no trace of blood, and rectal re-examinations of the patients who had markedly dilated hemorrhoids revealed a subsidence of the dilatation.

Prostigmin®, which has been found to have a coordinating propulsive action on the bowel (17) has long been used for post-operative atony (18), megacolon (19), and so-called left-sided constipation (2, 15f, 16). More recently Urecholine® has been used in post-operative and post vagotomy gastric and urinary retention (20), in megacolon (20d, 21) to counteract the side effect of hexamethonium given to hypertensive patients (22), and in constipation (16a, 23). Since Urecholine® has been available in oral tablet form for only a few years, this study afforded an opportunity to compare the two parasympathomimetic drugs as ambulatory medication. Unfortunately, many of the patients to whom Urecholine® was given could not complete the study, but the beneficial effects observed in a few patients seem to justify reporting here.

One of the parasympathomimetic drugs was administered to eleven patients in the army and civilian groups. One patient showed no improvement on oral doses of Prostigmin® up to 30 mg. four times daily or Urecholine® 25 mg. three times daily, each over a period of ten days, and on two occasions supplemented by a morning injection of the drug currently being given orally. Another soldier did not respond to four daily doses of 30 mg. of Prostigmin® or 10 mg. of Urecholine®, each for one week. Because both of these patients were recommended for separation from the service by the psychiatric section, it was not possible to study these patients on increased doses.

When dehydrocholic acid had failed in a 35 year old housewife and a 17 year old soldier, both of whom had a lifelong history of bowel evacuations only after enemas, oral Prostigmin 15 mg. with meals was substituted. This produced in both patients a sensation which they had not previously known—the urge to defecate. Addition of dehydrocholic acid softened their stools and decreased straining. Both patients were maintained on the combined therapy, the housewife for more than four years, with continued excellent results.

One soldier who had had poor results with six dehydrocholic acid tablets daily was given in addition oral Prostigmin® 15 mg. three times daily for a week, then twice daily for a week, then none. Decholin® was continued. During a follow-up period of three months after the initiation of the Prostigmin® therapy, the patient had, almost daily, softer stools. Thus, Prostigmin® aided in establishing more normal bowel habits which were maintained by continued administration of dehydrocholic acid.

A 56 year old housewife had to discontinue Prostigmin® because even with a dosage of 15 mg. once daily she complained of muscle and tongue tremors. A 17 year old soldier had nausea and headache after two days of therapy on 5 mg. of Urecholine® three times daily, with no effects on frequency of bowel movements. Both of these patients had subsequent moderate improvement on dehydrocholic acid alone.

One soldier was successful in having daily movements while taking dehydrocholic acid 0.25 Gm. three times daily, but he did not return to the clinic and had no medication for two weeks. During this time he had no bowel movements. He was then given Urecholine® 5 mg. three times daily, with equal success—daily movements after four days. Urecholine® was continued for three weeks, with resultant daily evacuations and no side effects. Reverting to dehydrocholic acid after this time produced no changes, and the patient had daily movements over the follow-up period of four months.

Another soldier had daily movements for three weeks while taking three doses of 0.5 mg. of dehydrocholic acid daily. Suddenly he had no movements without an enema. After two weeks he was given in addition Urecholine® 10 mg. three times daily, resulting after three days in daily movements without resort to enemas. After one week the Urecholine® was reduced to 5 mg. three times daily for another week, then it was discontinued. The patient had daily movements over the next two months with dehydrocholic acid alone.

CONCLUSIONS

Constipation is a very common symptom, and has been the subject of many reports in the lay (24) literature as well as in the medical literature since Hurst's classic book (25). It is a disorder which is found in all age, social, and environmental groups. Constipation is often related to an emotional or training pattern set up in childhood and usually is on a functional basis. Varia-

tions in clinical and laboratory findings are not predictable after hearing the patient's complaints.

Functional constipation, which in this group of patients had not previously responded to dietary measures and exercise, was amenable in most cases (80.9% of patients in this study) to a readily available, inexpensive, physiologic stimulant to evacuation, namely, dehydrocholic acid. Side effects are minimal and often the dosage may eventually be reduced as a more normal bowel habit has been established. The aim in modern therapy of constipation is ease of evacuation without emphasis on regularity or frequency.

Supplementary diet therapy and medications, as well as psychotherapy, if indicated, will help to correct the patients' symptoms and relieve the emotional strains related to their constipation, in order to make them more efficient individuals. The patients have been relieved of their discomfort, and a constipation-fixation has been removed.

In some patients the necessity for administering one of the parasympathomimetic drug arises. Oral Prostigmin® and Urecholine® have been found to be effective in these more seriously affected patients.

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ULCERATIVE COLITIS LESIONS IN IRRADIATED RATS*

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NONSPECIFIC ulcerative colitis of the most common determinate type has as its earliest recognizable lesion the formation of crypt abscesses in the colonic mucous membrane. The rupture of these abscesses into the submucosa and their coalescence produce the gross ulcers and the clinically evident disease. Crypt abscesses are not pathognomonic of ulcerative colitis, since they are observed in occasional autopsied human cases of amebic dysentery, lymphopathia venereum and severe vitamin deficiency (1). However, crypt abscesses are sufficiently characteristic of ulcerative colitis that knowledge of their etiology would be valuable in understanding what brings on this distressing disease. The production of genuine ulcerative colitis lesions of crypt abscess type in experimental animals has not previously been achieved. Some intestinal abnormalities seen in rodents treated with folic acid antagonists are vaguely reminiscent, but do not have the basal location and the polymorphonuclear masses which distinguish crypt abscesses.

In a large series of parabiotic rats used to investigate whether radiation reactions were mediated by circulating toxic substances (2), a minority of the irradiated parabionts developed typical microscopic crypt abscesses in the colon and lower small intestine. The changes in these and other mucous glands simulated human ulcerative colitis lesions closely enough to encourage reporting the observations.

MATERIALS AND METHODS

From a total of 346 parabiotic rat pairs prepared for radiation experiments, as previously reported, 38 pairs with complete autopsies and 72 additional pairs in which one partner had been adrenalectomized prior to irradiation and later autopsied were available for analysis. The rats selected for parabiosis were of Slonaker strain, and matched by sex, weight and usually by littermates. The operative technique used, demonstration of adequate vascular interchange and irradiation factors are given elsewhere (2).

Total body irradiation was administered, always to the right-hand partners, in single doses of 400, 800, 1200 or 1600r. Eighteen single control rats were similarly irradiated at one of these dose levels. After irradiation, the animals were killed at intervals of 1 hour to 29 days and complete autopsies performed. Reports of the general findings (2), endocrine changes (3), and the hematopoietic (4) or other abnormalities due to incompatibility and the development of hypersensitivity, producing so-called parabiosis intoxication (5), have previously appeared.

Total individual rats examined pathologically in each category are shown in Table I. For each irradiated parabiont rat the protected partner was also examined pathologically with equal care.

RESULTS

Crypt abscess lesions were found in 10 of the total 238 rats examined. No lesions of this type were found in protected parabionts, or in nonirradiated controls (Table II).

One control female rat, irradiated with 1600r 4 days before sacrifice, had crypt abscess lesions, that is 1 of 18 control rats (6%) or 1 of 7 female controls (14%

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TABLE II

OCCURRENCE OF CRYPT ABSCESS LESIONS

Irradiated rats	Total	800r		1200r		1600r	
		M	F	M	F	M	F
Single controls	18	0	0	0	0	0	1
Normal parabionts	38	0	0	0	0	1	1
Adx. parabionts	33	0	1	0	1	2	1
Parabionts, partner Adx.	39	0	0	0	0	1	1
Totals	128		1		1	4	4

TABLE I

TOTAL IRRADIATED ANIMALS EXAMINED FOR CRYPT ABSCESS LESIONS

Irradiated rats	Total	400r		800r		1200r		1600r	
		M	F	M	F	M	F	M	F
Single controls	18	5	2	3	2	1	0	2	3
Normal parabionts	38	8	4	6	9	2	0	5	4
Adx.* parabionts	33	4	3	3	6	3	7	5	2
Parabionts, partner Adx.*	39	5	4	5	5	5	3	4	8
Totals	128	22	13	17	22	11	10	16	17

*Adx. means adrenalectomized

of females). Two irradiated normal parabiont rats, one each male and female, had similar lesions 5 and 3 days respectively after 1600r; or 2 of 38 such animals (5%).

Seven hemiadrenalectomized pairs showed crypt abscess lesions in the irradiated partner. Five of these pairs had crypt abscess lesions in the irradiated and adrenalectomized partner, including 3 females, respectively 2 days after 800r, 2 days after 1200r and 4 days after 1600r; and one male each respectively 2 and 3 days after 1600r. The overall incidence in the subgroup of adrenalectomized-irradiated rats was 5 of 33 or 15%, and 3 of 18 such females (17% of females). Also one irradiated male and female each from pairs with adrenalectomy of the protected partner, 5 days after 1600r in each instance, had colonic crypt abscesses. This represented 2 of 39 or 5% of this rat subgroup.

Among the 10 rats with crypt abscess lesions, all of which had been irradiated, there were 6 females, and 7 were from hemiadrenalectomized pairs. The incidence of 9% crypt abscesses among all irradiated parabiotic rats was similar to that found in single irradiated rats, with incidence by sex 10% of females and 6% of males.

Microscopically all the animals with crypt abscesses demonstrated severe radiation damage, particularly to lymphatic tissues, small intestinal epithelium, gonads and bone marrow. The 10 rats with crypt abscesses had in addition a shrinkage and distortion of intestinal mucosal cells with pyknotic or fragmented nuclei, dilatation of crypts and foci of necrosis. Mitoses were scanty or absent. Beginning regeneration of intestinal mucosa was evident 3 days or later after 1600r.

In those animals with intestinal crypt abscesses and available salivary gland material, there was an abnormality of the salivary mucous cells, consisting of a coarse granularity of both intra- and extracellular mucin. Serous and duct cells had vacuolated cytoplasms, and less regularly a similar vacuolization and swelling were observed in gastric chief cells, duodenal epithelium and pancreatic acini. Similar epithelial changes have been found in the esophageal, gastric and intestinal glands of human cases of crypt abscess colitis (1).

Endocrine glands showed abnormalities beyond that expected from radiation damage alone. In the single control rat and the animals from irradiated pairs with normal complements of adrenal glands, there was microscopic adrenal cortical and medullary necrosis with loss of lipoid, exceeding that which uniformly occurred postirradiation in these groups of animals. In the hemiadrenalectomized pairs, the remaining adrenal glands, whether irradiated or protected, showed evidences of severe functional strain including marked depletion of cortical lipoid and decreased staining for free carbonyl groups, using the Ashbel-Seligman method (3). Cytological and histochemical evidence available thus supported a temporary hypoadrenocortical function state, which was most striking at the higher levels of radiation dosage.

It was of interest that while only 17 of 45 irradiated female parabionts had ovarian corpora lutea (38%), 4 of 5 female cases with crypt abscesses had corpora lutea (80%). In two of three crypt abscess cases in females, with available salivary gland material, there were found cytoplasmic granules in the eosinophilic salivary ducts, supposed to occur only in males (6). The case without salivary duct granules also had no corpora lutea. Corpora lutea are known to be equally or more radioresistant than the adrenal cortex.

Pituitary glands in the same cases had abundant or increased basophilic cells, as seen with gonadotropin and ACTH production (3). Hypersensitivity lesions of parabiosis intoxication (5) were observed in 1 of the 10 rats with crypt abscess formation.

DISCUSSION

Crypt abscesses developed postirradiation in 9% of parabiotic rats, in which a complicated variety of concomitant processes was occurring. These included 1) radiation necrobiosis and necrosis, 2) reparative mucous membrane regeneration, 3) endocrine imbalance, a) secondary to ovarian follicular destruction, decreased pituitary inhibition and resulting increased gonadotropin secretion, b) following hemiadrenalectomy, evident inadequacy of one pair of irradiated adrenals to supply the needs of both partners, or temporary adrenal hypofunction, 4) infection, an important complication of radiation disease, and 5) hypersensitivities developing between incompatible partners (2-5).

The time when crypt abscesses occurred was not that of the maximal irradiation damage, which suggested that the lesions were not directly attributable to radiation, except as it provided a trigger stimulus. Infection localized within the crypts of intestinal glands without an equal involvement of mucous surfaces or submucosa did not seem likely, has not been reported by others, or observed by ourselves. Hypersensitivity, while common in hemiadrenalectomized pairs, had no tendency to produce any mucous membrane lesions.

Studies of human and animal gastrointestinal tissues after ionizing radiation, as reported by Warren and Friedman (7), Mulligan (8) and others do not describe crypt abscess formation. Such lesions have not occurred in recent material collected to investigate the cytologic and histochemical alterations of irradiated intestinal epithelium (9, 10).

No correlation was possible with the incidence and localization of hypersensitivity lesions (5). Only 1 of the 10 affected animals had evidence of parabiosis intoxication.

The explanation seemed logically to lie in an abnormal regeneration and metaplasia of mucous cells in various sites, following injury, encouraged and possibly stimulated by an abnormal endocrine environment. Visibly granular altered aggregates of intracellular mucoprotein were observed, which became actively leukotactic upon secretion. The majority of the involved animals were females, and most of these had ovarian corpora lutea, which were little affected by radiation. In the presence of a cortical hypofunction of the adrenals inferred from the cytologic loss of lipoid and decrease in carbonyl groups, corpus luteal hormonal activity likely influenced glandular functions, and permitted among other things the masculinizing effects observed in the salivary ducts. Pituitary cell counts indicated a state of functional activity. In male animals with crypt abscesses normal granules were still found in these eosinophilic ducts. Testicular interstitial cells are usually considered responsible for the normal sexual dimorphism of rodent salivary

ducts (6). The enzymatic mechanism of this endocrine-induced dimorphism or metaplasia is as yet unknown.

In brief, it appears that the crypt abscess lesion most characteristic of one type of ulcerative colitis developed following radiation injury to mucous membrane cells, particularly in animals with adrenal cortical hypofunction but having a normal androgen or progesterone secretion. Whether these endocrine abnormalities tended to activate the proteolytic enzymes including mucinases which have been found to be increased in human ulcerative colitis (11) has not been determined. The steroid hormone imbalance inferred need not specifically involve progesterone. Other variations of adrenal corticosteroid production might account for male, prepubertal and postmenopausal cases of crypt abscess colitis.

Experimental investigations employing chemical, mechanical or bacterial injury to colonic mucosa in adrenalectomized animals injected with testosterone or progesterone would be of interest in further analysis of this mechanism of crypt abscess formation.

SUMMARY

Crypt abscess lesions, such as occur in one type of human ulcerative colitis, were observed in 9% of a large series of irradiated parabiotic rats. Affected animals also showed following radiation injury a metaplastic granular abnormality of mucus-producing cells in salivary glands and gastrointestinal tract. Temporary hypofunction of the adrenal cortex in rats with a normal activity of ovarian corpus luteal or testicular interstitial cells was considered to encourage the development of intestinal crypt abscesses.

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CLINICAL EVALUATION OF A SUSTAINED RELEASE BELLADONNA PREPARATION

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THE SIDE EFFECTS of effective doses of belladonna are frequent and annoying, particularly to the nonhospitalized patient. Consequently, while atropine and belladonna remain the standards of reference for antispasmodic activity, they have been abandoned clinically by many physicians in favor of synthetic anticholinergic agents.

Milligram for milligram, however, none of these substitutes equals atropine in physiological activity, and none is free of side effects.

This report concerns a new approach toward countering the disadvantages of belladonna. It consists of a novel dosage form called a Spansule capsule through which it was postulated that a conventional combination of conventional belladonna alkaloids could be released slowly and evenly in the gastrointestinal tract. Theoretically this would reduce side effects by eliminating peaks of absorption following ingestion of the drug. In addition, since these sustained release capsules were designed to maintain therapeutic levels of the alkaloids for 8 to 10 hours, other advantages particularly desirable in antispasmodic therapy were theoretical possibilities. The most obvious of these are convenience and prevention of nighttime breakthrough; a characteristic problem with hypersecretors.

The principle of sustained release medication has been applied successfully to amphetamines (1) and antihistamines (2, 3). The pharmaceutical form has been described by Green (2) in connection with the latter. Basically, it consists of a capsule containing a large number of minute pellets each containing a tiny divided dose of the medicament. From some of the pellets the drugs are released immediately to produce the initial therapeutic effect. About two thirds of the total dose, however, is divided among coated pellets with varying rates of release. The large number and the controlled proportion of the variously coated pellets thus provide a smoothly sustained release of the drug.

The success reported when this dosage form was applied to other types of medication coupled with the particular advantages it might offer in antispasmodic therapy seemed amply to justify a clinical investigation.

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Submitted Nov. 9, 1954.

MATERIAL AND METHODS

The Spansule capsules* used in this investigation contained belladonna alkaloids and phenobarbital according to the following formula:

atropine sulfate	0.06 mg.
scopolamine hydrobromide	0.03 mg.
hyocyamine sulfate	0.31 mg.
total alkaloids	0.4 mg.
phenobarbital	1.0 gr.

The clinical material consisted of 30 private patients whose age, sex, pertinent history, and diagnosis are shown in table 1. Patients were studied during the winter of 1953-54. Duration of treatment ranged from 10 to 29 weeks; the average being 18 weeks. In all ulcer cases listed, diagnosis was confirmed by x-ray. Possible ulcer cases for whom x-ray findings were not available are classified in more general terms (i.e., gastritis, tension syndrome).

This was a clinical impression study; hence certain disadvantages were unavoidable. Placebos were not used and evaluation of results was, of necessity, subjective. Within the limits of the method, however, every effort was made to remain, if not objective, at least impartial.

Because the gastrointestinal dysfunction in this type of patient usually produces obvious physical symptoms (i.e., pain, eructations, etc.), certain conclusions are possible on the basis of symptomatic response alone.

*Prydonnal Spansule capsules supplied for investigational use by Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

TABLE I

SUMMARY OF PRE-TREATMENT DATA

Patient	Age	Sex	Diagnosis	Previous Therapy	Comment
CS	51	M	Duodenal ulcer	alkalis, diet	poor response to previous therapy
AP	43	M	Pylorospasm	effervescents	
JR	51	M	Duodenal ulcer	diet, antispasmodics, psychotherapy	poor response to previous therapy
WS	33	F	"Spastic stomach"	diet, antispasmodics	
JJ	42	M	Chronic pancreatitis	antispasmodics	poor response to previous therapy
ES	28	F	"Spastic stomach"	diet, antispasmodics	poor response to previous therapy
IR	54	M	Duodenal ulcer	diet, alkalis, antispasmodics	
HH	29	M	Tension syndrome	antispasmodics, etc.	ditto—patient displaced German engineer
TB	61	M	Duodenal ulcer	antispasmodics, antacids, etc.	
CP	72	F	Pylorospasm	diet, alkalis	poor response to previous therapy
MM	44	F	Duodenal ulcer	diet, frequent feedings, etc.	
JC	37	M	Duodenal ulcer	diet, alkalis, antispasmodics	
HB	24	F	Pylorospasm	diet, alkalis, antispasmodics	
EO	31	F	Tension syndrome	alkalis	marital problems contributing factor
WR	33	F	Tension syndrome	no previous therapy	
NM	73	F	Gall Bladder	diet, antispasmodics, bile preparations	
ALeC	49	M	Tension syndrome	diet, antacids	patient is high pressure attorney
JC	49	M	Duodenal ulcer	antacids, antispasmodics	
AA	43	M	Tension syndrome	diet, antispasmodics	
GLaB	28	M	Tension syndrome	no previous therapy	
WL	44	M	Duodenal ulcer	antacids	
EC	52	F	Gastric ulcer	no previous therapy	
MK	70	F	Gastritis	antispasmodics, diet	
BC	59	F	Pylorospasm	alkalis, diet, sedatives	also psychotherapy—intermittent relief
FC	38	F	Tension syndrome	no previous therapy	
JG	68	M	Gastritis	diet, antacids, antispasmodics, etc.	poor response to previous therapy
MM	60	F	Duodenal ulcer	diet, antacids, antispasmodics, etc.	poor response to previous therapy
TM	41	F	Tension syndrome	no previous therapy	family problems contributing factor
HD	65	M	Duodenal ulcer	diet, alkalis, etc.	
GC	56	M	Duodenal ulcer	no previous therapy	patient is MD—not treated till hemorrhage required hospitalization, etc.

Relief of clinical symptoms was used, therefore, as the fundamental criterion of efficacy. No attempt was made at laboratory measurements of antisecretory or spasmolytic effects or at x-ray studies of the degree of healing in demonstrated ulcer craters. Because these criteria could not be utilized, the scope of the investigation was limited to the following questions:

1. Is the Spansule capsule effective in producing symptomatic relief and does its effectiveness persist long enough to make it a practical replacement for conventional t.i.d. dosage?

2. Is there an appreciable reduction in incidence and/or severity of side effects?

3. Is the effect of a bedtime dose sustained throughout the night?

4. Does the symptomatic improvement obtainable with this dosage form equal or exceed the response to conventional belladonna therapy?

Complete histories were taken on each patient—many of whom had been under our care for a considerable length of time and were well known to us. Data were recorded systematically on case report forms. Results were classified as follows:

excellent — complete symptomatic relief persisting at least 8 hours and not accompanied by side effects.

good — a similar duration and degree of relief but accompanied by mild side effects or somewhat less dramatic relief without side effects.

fair — appreciable but not superior relief or good relief accompanied by moderately severe side effects.

poor — no appreciable relief or prohibitive side effects.

Criteria of response consisted of the patients' comments and our own observations.

The usual dosage consisted of one Prydonnal Spansule capsule before breakfast and, when night pain was a problem, a second capsule before retiring. Bland diets were prescribed concurrently.

Results

The over-all results are summarized in table 2. By almost any standard, they are remarkably good. Response was rated excellent in 18; good in 8, fair in 1 and poor in 3. In all, (86%) of the patients treated obtained good to excellent results. Night pain was controlled in 16 of the 19 patients in whom it was a problem. Patient acceptance, on the whole, was excellent. The simplicity of the dosage in contrast to the usual multidose regimens served to increase the enthusiasm of patients with long experience on ulcer therapy. The response described below is typical:

> Patient I. R.: A 54 year old business man with a 20 year "classical" history of peptic ulcer. Previous therapy, consisting of the usual diets, antacids, and antispasmodics, had met with moderate intermittent success. On Prydonnal Spansule capsules, he reported prompt and sustained relief from both daytime and nighttime pain. Regarding the latter he remarked that he had "never slept like this before." This patient was followed on the medication for approximately 3 months during which he experienced no side effects and remained free of all symptoms of gastrointestinal dysfunction. He summed up his opinion of the medication as "wonderful . . . worth all the money in the world."

As noted, responses were classed as 'poor' or 'fair' in a total of four patients. In only one of these (HB), were side effects the deciding factor in the rating. Night pain was controlled in this patient by one Spansule capsule given before retiring. However, the therapeutic effect of the daytime dosage was vitiated by side effects of dry throat and drowsiness and the over-all response could be considered only fair. Generally, however, the severity of the side effects encountered was slight. They occurred in a total of 6 patients and consisted of drowsiness, dry mouth and throat, and blurring of vision. It is notable that only one patient reported blurring of vision and only two reported dry mouth and/or throat.

The three patients in whom night pain was not controlled were the only ones in whom the therapeutic effect of these Spansule capsules did not equal or surpass the conventional t.i.d. or q.i.d. dosage regimen.

TABLE II

RESPONSE TO PRYDONNAL SPANSULE CAPSULE THERAPY

Diagnosis	Number of Cases	Average Duration of Treatment (wks.)	Results			
			Excellent	Good	Fair	Poor
Proven ulcers	12	19	8	2		2
Pylorospasm	4	14	1	1	1	1
"Spastic Stomach"	2	13	1	1		
Chronic Pancreatitis	1	18	1			
Gall Bladder	1	20	1			
"Tension Syndrome"	8	18	5	3		
Gastritis	2	20	1	1		
Totals	30	18	18	8	1	3

DISCUSSION

The very excellence of these results leads one to re-examine and reconsider factors which might have contributed toward enhancing them. Undoubtedly the novelty of this dosage form, its convenience, and the ingenious mechanism through which it acts contributed to the patients' enthusiastic acceptance of it. Whether this contributed an appreciable placebo effect is impossible to determine in retrospect. Assuming that it did, however, the percentage of good or excellent results is still too high to be deprecated on these grounds. It would certainly seem desirable to investigate this preparation more thoroughly. Objective measurements of antisecretory and antimotility effects and maximum tolerated dosage are particularly needed before its ultimate clinical value can be determined. On the basis of limited clinical experience, however, it would seem that all four of the questions proposed above could be answered in the affirmative.

SUMMARY

1. A new sustained release dosage form of belladonna alkaloids called Prydonnal Spansule capsules was evaluated in 30 private patients with assorted gastrointestinal complaints, 12 of whom had proven peptic ulcers.

2. Excellent results were obtained in 18 patients; good results in 8; fair in 1; and poor in 3.

3. Night pain was controlled in 16 of 19 patients in whom it was a problem.

4. Side effects, consisting of 4 cases of drowsiness, 1 of blurring of vision, and 2 of dry mouth occurred in 6 patients.

5. On the basis of clinical observation, the preparation appeared to maintain effective therapeutic levels for from 8 to 10 hours following ingestion, to effectively control night pain in hypersecretors, and to produce an appreciably smaller incidence of side effects than conventional t.i.d. belladonna therapy.

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ABSTRACTS ON NUTRITION

JHATAKIA, K. U. AND DAMANY, S. J.: *A few observations on the nature and etiology of anemias.* J. Indian Med. Assn., 24, 4, Nov. 16, 1954, 129.

One hundred cases of anemia seen during a 2 year period at Sir J. J. Hospital, Bombay, are analyzed. It was found that 72 percent of cases depended upon faulty nutrition, while 10 percent were due to ankylostomiasis. The rest were due to hemolysis or open hemorrhage. Sixty cases were of macrocytic type and 35 cases were of microcytic type. No case of definite pernicious anemia was found in this group. In most of the macrocytic cases no megaloblastic reaction of the bone marrow was found. In 52 cases blood plasma proteins were below 5 gms. and this kind of hypoproteinemia undoubtedly is related to the type of anemia found. Apparently, however, not all the nutritional macrocytic anemias are due to one common factor, but of 75 gastric analyses done, only 12 cases showed complete achlorhydria, though histamine injection was done in only 2 cases.

BURNS, C. AND PRIOR, I.A.M. *Oral treatment of pernicious anemia.* New Zealand Med. Jour., 53, 297, Oct. 1954, 476.

Using "Bifacton" (an Organon Laboratories' tablet containing both vitamin B_{12} and intrinsic factor) by mouth, the authors were able to produce excellent reticulocyte responses and also increases to normal in the hemoglobin levels and red blood cell counts within 60 days. Improvement in cord changes has, however, been slow. The details of four cases are presented. Two tablets of "Bifacton" were given daily to each patient. One would judge that this medication would be satisfactory for uncomplicated cases, at least.

PAULSON, M. AND HARVEY, J. C.: *Hematological alterations after total gastrectomy. (Evolutionary sequences over a decade).* J.A.M.A., Dec. 25, 1954, 1556.

In studying the effects of total gastrectomy on erythropoiesis in 27 patients at varying intervals over a decade, the evolutionary sequences found were: first, an iron deficiency anemia, shortly after operation, associated with blood in the stools, and ascribed by the authors to the blood loss from ulcerated areas at the anastomotic site. Ferrous salts given orally corrected this anemia. Next, macrocytosis of the red blood cells (without anemia) occurs in one to two years after operation, if the patients live long enough. This is always followed by anemia and, still later, by the development of megaloblasts in the bone marrow. In patients in whom this macrocytic-megaloblastic type of anemia develops, response is obtained from the parenteral administration of vitamin B_{12}. Patchy jejunal atrophy not unlike the gastric atrophy seen in pernicious anemia has been encountered and may play a role in the development of this primary anemia. The authors do not mention glossitis nor cord changes, nor do they state that this advanced anemia actually signifies the Addisonian disease.

MARQUES, R. J.: *Skin and oral lesions, attributable to nutritional deficiency, associated with cirrhosis of the liver.* Amer. J. Gastroenterology, 22, 6, Dec. 1954, 472.

Marques, professor of clinical medicine, the Medical-Science School of Pernambuco, Brazil, describes hyperkeratotic and xerotic lesions of the skin with pigmentation found in Brazilian persons with hepatic cirrhosis

in the ascites stage. Various types of glossitis were encountered. The legs and arms were chiefly affected, sometimes with "crazy pavement" types of lesions. Whatever the cause of these lesions, Marques thinks their frequent occurrence in patients with cirrhosis of the liver should be emphasized. They suggest that the patients are in an advanced stage of malnutrition and indicate the usefulness of vitamin treatment in hepatic cirrhosis.

COPPELL, D. F., HUTCHISON, H. E., HENDRY, E. B. AND CONWAY, H.: *A new carbohydrate-iron hematinic for intramuscular use.* Brit. Med. J., Nov. 27, 1954, 1255.

A preliminary account is given of the successful clinical trial in 15 patients of a newly elaborated proprietary dextran-iron hematinic ("Imferon") (Benger's Ltd.). The agent proved non-irritating when given intramuscularly and was readily absorbed, giving serum iron levels of 600 micrograms within 18 hours. Absorption via the lymphatics was demonstrated histologically. The complex proved an effective hematinic, giving average hemoglobin regeneration rates of between 3.5 and 11.3 percent Hgb. per week over the first 4 weeks of treatment. The patients' iron deficit was calculated approximately on the basis that 100 mg. Fe is equivalent to 4 percent Hgb. (There is some risk of permanent skin pigmentation at the site of injection).

WEBER, F. P.: *Case of achlorhydric anemia in a male followed up for 20 years.* Brit. Med. J., Dec. 25, 1954, 1529.

At age 32 a salesman was found to have a severe anemia and histamine fast achlorhydria, although pepsin appeared in the gastric juice after histamine injection. The anemia showed a color-index less than unity. The smear picture was notable for anisocytosis and poikilocytosis. Bone-marrow puncture revealed a megaloblastic reaction. He had glossitis at times. There were never any definite signs of subacute combined degeneration of the spinal cord. Early in his treatment reduced iron and an acid-pepsin mixture produced good remissions. Later he did better on liver extract. Simple microcytic anemia could be ruled out. For several reasons, a diagnosis of Addisonian pernicious anemia could not definitely be made. Striking features of his case were mental depression, feelings of unreality, and symptoms resembling temporal lobe epilepsy and schizoid manifestations. Electric convulsive therapy, done on many occasions, always caused improvement.

DAVEY, D. A., FOXELL, A. W. H. AND KEMP, T. A.: *Treatment of hemochromatosis by repeated venesection.* Brit. Med. J., Dec. 25, 1954, 1511.

Repeated venesection is now being used in the treatment of hemochromatosis with favorable results. The idea is to deplete the iron stores by withdrawing blood and thus prevent the later disturbances which result from fibrosis of various organs. A case is reported in whom 55 pints of blood were removed over the course of two years. At the end of this time a severe anemia developed which is thought to be due to exhaustion of available iron stores. Some subjective and objective improvement has occurred in spite of the anemia. It appears that venesection is an effective means of treating selected patients with this disease.

EDITORIALS

TWO OF THE MOST DIFFICULT DIAGNOSES

Perhaps duodenal ulcer and early cancer of the left colon stand out as two of the most difficult diagnoses which we are called upon to make.

While the pain-food-relief complaint is highly characteristic of duodenal ulcer, it is by no means invariably present, and we know today that some patients in whom craters can be demonstrated have no symptoms of any kind. In such cases we may assume that the ulcer is in a passive, or painless stage. No convincing explanation for these "dormant" ulcers has ever been presented. (In this connection it is at least debatable whether or not such a painless ulcer should be subjected to the usual ulcer regime).

Quite commonly one is convinced by the symptoms that a peptic ulcer is present but repeated x-ray examination fails to reveal objective evidence of its existence. Unfortunately there are still a few roentgenologists who, aware of the symptoms, customarily stretch their imagination while studying spot films, and make a positive report of ulcer just to be on the safe side. Certainly it is the duty of a roentgenologist to make a negative report when the findings actually are negative, but naturally this ought not to influence the referring physician too much, if he himself is convinced that an ulcer is present. If there were no x-ray machines in existence, it is likely that peptic ulcer could be diagnosed with reasonable probability of correctness merely from the patient's story. In the diagnosis of ulcer, a well-taken history, with assessment of the patient's personality traits is of greater value than a poorly-made x-ray examination of the stomach and duodenum. When the physician is convinced that an ulcer is present, he should treat it as such, provided no other objective findings can explain the symptoms, and even though the roentgenologic report is negative. Should the use of the ulcer regime fail to improve the symptoms, we may be dealing with habitual hypoglycemia or merely a spastic colon, the latter being a fairly constant association with ulcer.

Increasing constipation usually is the first symptom of cancer of the left colon, but here the barium enema may be of no assistance in the early stages, and even spot films taken at various levels of the descending colon may show nothing. The sigmoidoscopic examination likely will be negative. No mass can be felt in the left side of the abdomen. There are no enlarged lymphatic glands in the inguinal region. There may or may not be a positive benzidine test on the feces. If this test is positive it will increase our suspicion of such a lesion.

In its early stages there probably will be no loss of weight, and anemia is uncommon. Later, when some palpable degree of obstruction occurs or when a constant filling defect is present, there is no longer any problem. Yet, even at this stage, the end results of surgery may prove to be bad because of metastases. For these reasons, if the clinician is persuaded that a malignant lesion exists in the left colon, even though *all* tests are negative, it is desirable, if not imperative, that exploratory laparotomy be done. Nevertheless, inasmuch as the patient may be elderly, and proof lacking, it is always difficult to induce a good surgeon to do such an operation. But unless exploration, under these conditions, is more frequently done, we are not going to obtain permanent cures in any except a small percentage of cases.

REMARKS ON THE MANAGEMENT OF PEPTIC ULCER

Occasionally the modern anticholinergic drugs appear to be superior to belladonna or atropine, but in general it is difficult to see that they possess any advantages in the treatment of peptic ulcer.

Many physicians, accepting the anticholinergic drugs as final, use them to the exclusion of sedatives and antacids. Under these circumstances the results frequently are not good, but improvement may result when the latter two types of drug are added to the treatment.

Possibly the majority of physicians have, by this time, concluded that the anticholinergic drugs have few advantages over atropine. It is quite certain that the anticholinergic drugs are not a cure-all in ulcer, and that their use does not bring about remission of ulcer symptoms any more quickly than the classical ulcer regimes.

No matter what drugs, what diets or what antacids are employed in ulcer treatment, it should be firmly borne in mind that the mental and emotional status of the patient is of first importance. This concept, long agreed to by the psychotherapists, is now subscribed to by an increasing number of internists and gastroenterologists. Subtotal gastrectomy or gastrojejunostomy with vagotomy may or may not bring long-lasting relief to the patient. But unless there is a drastic revolution deep within the recesses of the patient's being, there can be no real cure of peptic ulcer.

In one's private practice, medical treatment more often fails than succeeds in bringing about a long-lasting remission. The results from surgery have been better, but there is an undetermined percentage of patients in which old symptoms persist or new ones begin. In a very few cases twenty year cures have been attained,—but always in persons capable of grasping the concept of tranquility. This lesson is hard to teach, but repeated conversations aimed at inculcating new mental attitudes are rewarding, provided the patient is intelligent and provided also that his interpersonal relationships do not present him with an unsolvable problem in chronic irritation.

BOOK REVIEWS

LA PETITE CHIRURGIE DES FISTULES ANALES. Jean Arnous and Ernest Parnaud. Masson et Cie, 120 Bvd. St. Germain, Paris 6. 1000 francs.

For the first time in French medical literature there appears a book on ambulant proctology, devoted to the minor surgery of anal fistula. Special emphasis is placed on the relatively new subject of glandular fistulas opening into the anal crypts. The surgical techniques described are suitable for almost all cases of fistula. Naturally the idea of ambulant surgery of this disease has strong social fascination.

PORTAL HYPERTENSION. THE DUMPING SYNDROME. Masson et Cie, 120 Blvd. St. Germain, Paris VI. 3500 fr.

This volume of nearly 500 pages is contributed to by several authors (some writing in English) and represents the reports of the Fourth Congress of the National European and Mediterranean Societies of Gastroenterology. Both subjects are adequately covered. The volume is well illustrated, and should be read by all American gastroenterologists who desire to obtain European viewpoints.

SURGERY OF THE CECUM AND COLON. Stanley Aylett, M. B., F.R.C.S., Williams & Wilkins Co., Baltimore 2, Md. $9.00.

Books devoted to the study of the large intestine are rare among English publications and one confined to the surgery of the cecum and colon has not previously appeared. Unusual attention is given to the anatomy and physiology of the organs involved, and diseases of the rectum are mentioned only incidentally. Particular attention is paid to the step-by-step description of operative technique, for it is upon this that success finally depends. The volume is well illustrated and can be most highly recommended.

FOIE ET REINS. R. Cachera, C. Betourne, F. Darnis, J. Hamburger and P. Tanret. Masson et Cie, 120 Bvd. St. Germain, Paris 6. 560 francs.

This volume deals theoretically and also practically with ascitis associated with hepatic cirrhosis as well as renal insufficiency. The subject is approached from the standpoints of the biologist, the radiologist, the surgeon or the specialist, in a lively symposium. Ignorance is profound in our knowledge of the true nature of cirrhotic ascitis. In renal insufficiency the chief emphasis is placed on protein metabolism and electrolyte balance.

GENERAL ABSTRACTS OF CURRENT LITERATURE

HUGHES, E. S. R.: *Carcinoma of the colon.* Med. J. Australia, Oct. 9, 1954, 577.

A study of 50 cases of colonic cancer shows that the lesion occurs most frequently in the rectum and sigmoid. The tumors are, on the whole, amenable to resection with good prospect of cure. In 32 of the present series a one-stage operation with wide resection and immediate anastomosis was performed with good prognosis for cure. Other cases had too much local spread of the malignant lesion. The average length of time between the onset of the symptoms and the operation was 4 months. Sometimes, in advanced cases, palliative resection alone was done. In 41 cases radical resection of the tumor and its lymphatic field was carried out. Occasionally, where acute obstruction was present, a colostomy or cecostomy was done as a preliminary step. Hughes says that with attention to all details the surgeon should be able to approach the excellent results being obtained with the one-stage operation at Saint Mark's Hospital, the Gordon Hospital, the Massachusetts General Hospital, the Lahey Clinic and the Mayo Clinic.

BARCLAY, S. AND MCINTYRE, J. H.: *Gastrectomy for ulcer.* New Zealand Med. J., 53, 296, Aug. 1954, 396.

A review of 64 cases of subtotal gastrectomy, all done by one surgeon, showed that 87 percent were completely satisfied with the results. Nine percent only were dissatisfied. Only one case of "dumping syndrome" was encountered. The almost total absence of significant after-toubles in these patients in New Zealand, as compared with the higher incidence of distressing syndromes reported from Great Britian, may well be related to the better nutritional status of the population, and particularly the availability of good quality protein and relatively low bulk foods.

GANS, B.: *The fallacy of the furred tongue.* Brit. Med. J., Nov. 13, 1954, 1147.

A deep-rooted belief exists in both lay and medical minds that a dirty tongue, in a child not suffering from an acute illness, is of significance. Statistical analysis of the state of the tongue in 750 children shows that there is no connection between a furred tongue and the state of the tonsils, the teeth, the presence of a free nasal airway, the presence of cervical glands or the action of the bowels. Similarly, no association can be demonstrated between the state of the tongue and a variety of abnormalities ranging from tongue-tie to tics and from murmurs to mongolism.

WELLS, C. AND MACPHEE, I. W.: *Partial gastrectomy: ten years later.* Brit. Med. J., Nov. 13, 1954, 1128.

The author made careful follow-up studies on 75 patients who had been treated for peptic ulcer by partial gastric resection 10 or more years previously. The incidence of recurring ulcer varies inversely with the extent of the gastric resection. With the Polya type of anastomosis, the incidence of bilious vomiting varies directly with the extent of the gastric resection. The authors found that serious post-gastrectomy symptoms may not develop until many years after the operation, and this applies both to anemia and vomiting. If direct gastro-duodenal continuity is not re-established at the time of the operation, hypochromic anemia is apt to occur. A more limited type of gastric resection combined with vagotomy and a gastro-duodenal anastomosis may represent the Aristotelian mean in the surgery of peptic ulcer.

CLARKE, C. A., AND MCCONNELL, R. B.: *Six cases of carcinoma of the esophagus in one family.* Brit. Med. J., Nov. 13, 1954, 1137.

A pedigree is presented showing 6 cases of cancer of the gullet in two generations. Since the disease is a relatively uncommon one, there are reasons for thinking that in this family the disease may have been due to a single dominant gene, although the part possibly played by environmental factors is mentioned. The authors hope that others will report any similar observations, since pooled information on families might be of great value in determining the factors responsible for this disease.

FIRNSCHILD, P.: *Splenectomies at Harper Hospital 1947-1953.* Harper Hosp. Bull., 12, 6, Nov.-Dec. 1954, 195.

Fifty-three splenectomies were done at Harper Hospital for a variety of reasons from 1947 to 1953. The biggest single reason for removing the spleen was to permit more radical operations in the left upper quadrant. One spleen was removed when it was found in the thoracic cavity during the repair of a diaphragmatic hernia. Two patients operated on with a preoperative diagnosis of lower abdominal mass, had their spleens lying in the lower abdomen with elongated pedicles. Other reasons for the operation were—trauma, abscess, thrombocytopenic purpura, congenital hemolytic anemia, primary hypersplenism and the group of secondary hypersplenism including Banti's syndrome, Gaucher's disease, Felty's syndrome, leukemia and lymphosarcoma.

MILLER, P. B. AND SANDWEISS, D. J.: *Perforation of a post-gastrectomy stomal ulcer during cortisone therapy.* Harper Hosp. Bull., 12, 6, Nov.-Dec. 1954, 199.

A patient who three years previously had had a subtotal gastric resection for a chronic duodenal ulcer was treated with large doses of cortisone because of chronic lymphatic leukemia. During the fourth week of cortisone therapy she developed evidence of small bowel obstruction. At operation, in addition to acute small gut obstruction, a perforated ulcer 2 cm. in diameter was found at the posterior aspect of the gastrojejunal anastomosis. The perforation was closed and she made a good recovery. During the 5 post-operative

days, while still on cortisone therapy, six gastric aspirations showed free HCl concentration varying in degree from 0 to 20 clinical units. A review of the literature fails to show a similar case of a stomal ulcer perforation during steroid therapy in a patient who previously had had a gastric resection for ulcer.

SMITH, L. A.: *The pattern of pain in the diagnosis of upper abdominal disorders.* J.A.M.A., Dec. 25, 1954, 1566.

By carefully worked out charts showing the site and radiation of pain in various upper abdominal lesions, Smith shows that an analysis of pain is as good a diagnostic tool as some other procedures that are more widely accepted. There are characteristic pain patterns in gastric, duodenal and gastro-jejunal ulcers; gallbladder and pancreatic disease; diaphragmatic hernia and in certain of their complications. With careful elucidation of a patient's story concerning the site and type of pain and also its time sequence, the pain pattern can be determined and the causative lesion suggested. The relation of this information to other findings will usually establish the diagnosis.

SENECA, H.: *The treatment of intestinal amebiasis with Magnamycin®.* Amer. Pract. & Dig. Treatment, 5, 12, Dec. 1954, 930.

In a series of 17 cases of chronic amebiasis treated with 10 to 12 Gm. of Magnamycin, 16 were cured clinically and parasitologically. In most of these cases, classical forms of treatment had failed and in some of them Terramycin treatment had not been effective. They were given 500 mg. doses three times daily after meals for 8 to 10 days. Most patients tolerated the treatment well, with minor side effects. Two patients developed nausea, one developed diarrhea, and a fourth patient developed perianal itching following the treatment. The patients have been followed for from 4 to 12 months. In one, cysts were subsequently found in the stools but disappeared on the use of Terramycin. It is possible that a combined treatment with Terramycin and Magnamycin would give superior results.

KAPLAN, M. H.: *Newer drugs in the management of peptic ulcer.* Amer. J. Gastroenterology, 22, 6, Dec. 1954, 439.

It has been the experience of the author and that of his associates that the anticholinergic drugs are useful as an adjunct in the management of peptic ulcer but have few advantages over the standard belladonna drugs. The untoward reactions have been sufficiently distressing to cause their use to be limited to the uncomplicated cases that do not readily respond to the previously accepted therapeutic agents.

FELDMAN, M.: *Further studies on prolapse of the gastric mucosa into the duodenum.* Amer. J. Gastroenterology, 22, 6, Dec. 1954, 444.

Up to 1954 there have been 146 published reports on prolapse of the gastric mucosa, with 1066 cases recorded. Of these, 209 were explored surgically. The condition is a clinical entity and produces symptoms suggestive of atypical duodenal ulcer. However, pain often is aggravated by food, alkalies sometimes fail to give relief, there is no night pain, it occurs oftenest in the older age group, usually hyperacidity is lacking, and there is a greater tendency to nausea and vomiting than in duodenal ulcer. The x-ray findings are pathognomonic of the condition. The incidence is approximately 10 percent of the adult population. It is usually a medical problem, and only in severe cases is surgery indicated. In the medical treatment, antispasmodics, anticholinergic drugs, diet and psychotherapy are the necessary measures. In the surgical treatment, when indicated, subtotal gastrectomy is the treatment of choice in most instances.

WINDWER, C. AND GEROFF, D. G.: *Cholecystogastrostomy of 28 years' duration.* Amer. J. Gastroenterology, 22, 6, Dec. 1954, 467.

The patient, a man 47 years old, had had a cholecystogastrostomy done 28 years previously because of jaundice, diseased gallbladder and stenosed common bile duct. Present tests give no indication of cirrhosis. There has been no evidence at any time of ascending infection or hepatitis. He developed a duodenal ulcer and has high gastric acidity, which proves false the old idea that bile was an efficient neutralizer of acid in the stomach. The gallbladder was not visualized by oral cholecystography because it drains so rapidly. The fistula still is present as seen in the barium x-ray series. In spite of mild dyspeptic symptoms the patient carries on. This may be the longest surviving case on record of an individual subjected to cholecystogastrostomy.

HUNT, J. N. AND KAY, A. W.: *The nature of gastric hypersecretion of acid in patients with duodenal ulcer.* Brit. Med. J., Dec. 18, 1954, 1444.

The authors assume that the maximum acid secreting power of the stomach is that degree of acidity which occurs in response to very large doses of histamine, (the patient being protected, by antihistamines, from the unfavorable general effects of the injected histamine). It was found that patients with duodenal ulcer have an abnormally high maximal secretory capacity, as compared with normal persons. It was also found that the development of stenosis in duodenal ulcer patients is associated with a *raised* maximal secretory capacity. Taking the normal group and the ulcer group, the maximal secretory capacity during basal secretion is not different. It is concluded that the basal hypersecretion of acid in duodenal ulcer can be accounted for by the increased maximal secretory capacity. It is not necessary to postulate an increase in excitation bearing on the parietal cells in patients with ulcer during basal secretion.

THOMAS, E. AND STEPHEN, P. M.: *Pancreatic calculi.* J. Indian Med. Assn., 24, 4, Nov. 16, 1954, 126.

In a review of biopsy and postmortem material for 11 years (1943-1953) at the Christian Medical College Hospital, Vellore, there was a total of 9 cases of pancreatic calculosis—3 surgical and 6 autopsy. There is thus a high incidence of one case in every 220 postmortems. The autopsy incidence is much higher than that reported by others. The chief complaints were colicky pains in the epigastrium with radiation in a few cases to the chest and lumbar region. In a few there was nausea, vomiting, diarrhea, steatorrhea and weight loss. Pre-operative x-ray diagnosis was made in 2 of the surgical cases.

O'Connor, F. J. and Ritvo, M.: *Diagnosis of hiatus hernia on plain roentgenograms of thorax and abdomen.* J.A.M.A., Jan. 8, 1955, 113.

Early and accurate diagnosis of hiatus hernia is of great importance as the condition may be confused with coronary disease, gallbladder disease and other serious lesions. The diagnosis after administration of a barium meal is an established procedure but it is not generally realized that many cases can be diagnosed from plain films of the chest, ribs, spine and abdomen. The lesion appears frequently in mass surveys where chest films are taken. The gas-filled portion of the herniated stomach is often plainly visible, sometimes superimposed on the cardiac shadow.

Stone, C. S. and Garrett, W.: *Operative cholangiography.* Bull. Mason Clin., 8, 3, Sept. 1954, 109.

In cases in which the common duct is not dilated it is usually unnecessary to do operative cholangiography or exploration. But in cases where dilatation is present, one or both types of investigation are called for, provided symptoms of colic are present. In cases in which, because of jaundice or colic or palpable stone, it is almost certain that calculi are present in the common duct, exploration is made without preliminary cholangiograms. Cholangiography is by no means foolproof and requires much experience for good results. If the medium used is too thick, stones may be obscured, especially when the stones are small. The authors describe in detail their procedures in doing cholangiography, but do not mention which medium they employ.

Molander, D. W., Friedman, M. M., and La-Due, J. S.: *Serum cholinesterase in hepatic and neoplastic diseases: a preliminary report.* Ann. Int. Med., 41, 6, Dec. 1954.

A special colorimeterical technique for serum cholinesterase has been devised which is accurate. Determinations were made on 20 patients with parenchymal liver disease and in 33 with metastatic cancer of the liver. Low values were found in patients with acute parenchymal disease, varying levels in those with chronic parenchymal disease, and low values in metastatic cancer and in lymphoma spreading to the liver. The serum cholinesterase levels may sometimes be the only evidence of malignant metastases to the liver.

Webber, R. J. and Rosser, R.: *Acid-peptic ulceration in schizophrenic patients during histamine treatment.* Journal-Lancet, Dec. 1954, 479.

Histamine was administered to 10 patients suffering from schizophrenia. Aqueous solutions were used first and followed later by histamine-beeswax injections. These injections were undertaken to determine if any improvement would result in the mental condition, inasmuch as it has been determined that histamine is the most efficacious agent for the dilatation of the cerebral arteries. The results were poor, and it was concluded that histamine did not produce any mental improvement. As a side result, it was found that 2 out of 7 patients who received the histamine-beeswax injections developed duodenal ulcer. In one of these cases perforation developed requiring surgery. The conclusion is obvious,—that in any cases where histamine injections are continued for several weeks, peptic ulceration should be watched for, or better still, prevented by the concomitant use of a Sippy regimen.

Gilbert, S. N. and Abrams, A. B.: *Pseudocysts of the pancreas: a modified method of drainage combined with cystogastrostomy.* Amer. J. Gastroenterology, 22, 6, Dec. 1954, 478.

The authors present a case of pseudocyst of the pancreas, retrogastric in position, occurring after ten years of recurrent, unrecognized attacks of pancreatitis. It is the fifty-first case recorded in the literature apparently cured by the internal drainage method of cystogastrostomy. The use of the Levin tube sutured into the cyst cavity through a stoma made in the posterior wall of the stomach is suggested as an aid to successful drainage.

Annomalai, A. L.: *Treatment of typhoid fever with levorotary chloramphenicol.* Jour. Indian Med. Assn., 24, 1, Oct. 1954, 9.

Eighty-five cases of typhoid fever were successfully treated with levorotary chloramphenicol tablets with no relapse. Complications due to the drug were nil, (2 cases of aphasia and 4 cases of intestinal hemorrhage were met with and treated successfully). Fluid and electrolyte imbalance and B-complex deficiency were anticipated and treated. The drug in tablet form is effective in small doses. Temperature usually returned to normal in from 48 to 96 hours. Patients were dismissed from hospital in 2 weeks and were back at work a fortnight later. The only death which occurred was as a result of intestinal perforation which had occurred prior to admission to the hospital.

Felson, B. and Levin, E. J.: *Intramural hematoma of the duodenum: a diagnostic roentgen sign.* Radiology, 63, 6, Dec. 1954, 823.

Intramural hematoma of the duodenum may be traumatic or spontaneous and its development is associated with acute abdominal symptoms which are nonspecific in nature. Gastrointestinal examination reveals a striking roentgen finding which is pathognomonic of the condition. The affected portion of the duodenum appears swollen, poorly filled with barium and presents a "blurred" appearance. Four cases are presented, in 3 of which surgical confirmation was obtained.

Ogilvie, T. A. and Shaw, H.M.: *Primary tumors of the small bowel.* Brit. Med., J., Jan. 15, 1955, 142.

The authors review the primary tumors met with in the small intestine and report a series of 16 cases dealt with over the past 10 years in the Essex County Hospital, Colchester. Adenocarcinoma is the commonest of these tumors, and the tumors occur most frequently in the duodenum and upper jejunum. Symptoms occur late owing to the fluid nature of the bowel content at this level. Prognosis is uniformly poor. Five cases of lymphosarcoma are included and it is suggested that in suitable cases resection of the involved segment, followed by x-ray treatment, is the best form of therapy. The carcinoid or argentaffin carcinoma is described.

FURADANTIN

Urinary tract infections in pregnancy is the subject of a study to be directed by Dr. Nicholson J. Eastman, obstetrician-in-chief at the Johns Hopkins Hospital, Baltimore. Dr. Paul F. Macleod, medical director of Eaton Laboratories, announced a $4,500 grant in support of the project, which will continue for a year. Furadantin (Eaton), an antibacterial urinary agent, is the first of the nitrofurans developed for systemic use and a determination of its effectiveness in such infections will be included in the study.

NEW UROGRAPHIC MEDIUM INTRODUCED BY WINTHROP

Hypaque Produces Very High Per Cent of Satisfactory Urograms

A new excretory radiopaque agent, which provides satisfactory x-ray films of the urinary tract in an unusually high percentage of cases with virtually no reported major side effects, has been introduced nationally by Winthrop-Stearns Inc.

The new contrast medium is called Hypaque. Prior to being made available to the medical profession, it was tested on several thousand patients in most of the important medical centers in the United States. The clinical reports indicate that Hypaque represents an important advance in terms of the quality of excretory urograms obtained, low toxicity and high tolerance.

Hypaque produced virtually no major reactions, and a minimal number of minor side effects, according to the studies. Of particular significance was the absence of vein cramp in 99 per cent of the cases observed. Previously, reports of vein cramp during excretory urography have not been uncommon.

Following intravenous injection, Hypaque is rapidly carried to the kidneys where it is eliminated. Excretion begins almost immediately in normally functioning kidneys, with most of the drug eliminated within two hours and over 90 per cent within 24 hours.

In a series of 210 cases studied at the University of Tennessee College of Medicine, 92.9 per cent of the films showed excellent or good views of the kidneys, ureters and bladder. The investigators, Drs. Thomas D. Moore and Raymond F. Mayer, found that 86.7 per cent of the patients experienced no side effects. Only minor reactions occurred in the remaining 13.3 per cent.

Commenting on their findings, the Tennessee doctors said:

"The complete absence of vein cramp was notable. There were virtually no vasomotor reactions, and none of the patients complained of bitter, metallic taste with Hypaque, in contrast to that commonly observed with some other excretory mediums."

A cooperative study of 1123 patients by 26 researchers revealed that 94.9 per cent of the urograms obtained were satisfactory for diagnostic purposes. Of that figure, 85.3 per cent of the films were excellent or good. Ninety per cent of the 1123 patients had no side effects.

It was found that a dose of 30 cc. of Hypaque sodium, 50 per cent solution, produced dense, sharp shadows in the vast majority of adult patients who had previously been partly dehydrated and effectively purged. Clearly defined shadows on film were often obtained five minutes after injection of Hypaque. Visualization of the urinary organs was usually best on films exposed five, ten and fifteen minutes after injection, the studies showed.

Hypaque was conceived and developed by the Sterling-Winthrop Research Institute. It contains 59.87 per cent iodine and is highly water soluble. Chemically, the drug is sodium 3,5-diacetamido-2,4,6-triiodobenzoate.

It is supplied by Winthrop-Stearns in a 50 per cent sterile aqueous solution, in 30 cc. ampuls.

CLEVELAND PHYSICIAN HONORED AS 100,000TH VISITOR TO TOUR PARKE-DAVIS LABORATORIES

Detroit.—A Cleveland physician was honored recently as the 100,000th professional visitor to tour the main Parke, Davis & Company manufacturing and research laboratories here.

Dr. Raymond J. Stasny (5644 Broadway, Cleveland) was greeted by Harry J. Loynd, Parke-Davis president, and John A. MacCartney, trade relations manager for the firm, as he began a two-day tour of the pharmaceutical company with approximately 60 other physicians from St. Alexis Hospital, Cleveland.

The 55-year-old general practitioner was presented with a special parchment scroll and was honor guest at a banquet in the Sheraton-Cadillac hotel.

"Parke-Davis has sought to keep physicians, pharmacists and allied professional groups informed of developments in its laboratories," Loynd told Dr. Stasny. "One method of spreading this information has been these tours of our manufacturing and research facilities, which have drawn us closer to members of the various health professions."

MacCartney pointed out that following the founding of the company in 1866, the tours were on an informal basis, but an organized pattern was established over 30 years ago. The tours have grown until today approximately 10,000 physicians, pharmacists, dentists, hospital personnel and upperclassmen from schools of medicine and pharmacy go through the laboratories each year.

While in Detroit, the visitors are guests of the 88-year-old company. They pay their own expenses to and from Detroit because, as one physician put it, "We feel this is an important part of our professional education."

MacCartney explained, "We would like to expand the tours to include others, but the 10,000 persons connected directly or indirectly with our business keep us busy."

The visitors come from all over the United States and virtually every country outside the Iron Curtain in groups ranging from two to 200. Many bookings are made six months to a year in advance for the opportunity to walk 10 miles through the Parke-Davis laboratories.

The two-day tour begins when the group is met by Parke-Davis chartered buses, which take them to a Detroit hotel. After breakfast, the visitors are whisked to the laboratories where approximately 100 escorts—whose regular jobs range from foreman to research scientists—take over, one to each group of seven or eight. During the first day, they see the manufacturing operations.

On the second day, different escorts take the visitors through the

research facilities. Parke-Davis was the first commercial institution in America to erect a building solely for the purpose of scientific research. At the conclusion of the tour, an open forum is held in a recently-constructed visitors lounge. Department heads sit on panels to answer all questions pertaining to the medical and pharmaceutical fields.

Depending upon the departure time, the group is given a reception, banquet and entertainment, either on the first or second night.

Many visitors have come back for the second and third 10-mile tour—commenting:

"We see something new each time!"

EDWARD RHODES STITT AWARD PRESENTATION

by

JOHN L. DAVENPORT

Executive Vice President
Chas. Pfizer & Co., Inc.
Brooklyn, New York

At Honors Night Dinner, Association of Military Surgeons of the United States, Statler Hotel, Washington, D. C., Wednesday evening, December 1, 1954.

It is a great honor and privilege to represent my Company tonight at the presentation of the first Stitt Award.

This occasion emphasizes the warm personal feelings my associates and I have, in being linked with an industry whose primary objective it is, to assist the medical profession in its herculean efforts to render the highest quality of medical service to the sick and suffering throughout the world.

Great deeds are being achieved by the medical profession of the United States. Our country has arisen to the forefront in virtually every field of medicine. This leadership has its foundation in freedom and opportunity—a freedom and opportunity which has rarely been accorded to man in his long history. Twenty-five hundred years ago, Socrates said: "One cannot get nearer to the gods than by giving health to his fellow men."

From such thoughts as this, has come the inspiration which has induced the great achievements of the medical profession in the last 25 to 50 years. In the time of Socrates and for hundreds of years thereafter, man could expect to live to the age of 22. Fifty years ago, he could expect to live to the age of 49. Today, you can expect to live to the age of 70. Who has made a finer contribution to life, liberty and the pursuit of happiness?

The awards that are being presented here tonight are really symbols of the great strides that have been taken in medical progress.

The Stitt Award, which our Company is pleased to add to your list of distinguished awards, has been established to recognize progress in the field of antibiotic medicine—a field that in the last decade has seen such a dramatic growth, but which still holds so much promise for the future. Your Awards Committee has stipulated that the award should go to that member of the Association of Military Surgeons who has made the most outstanding contribution in the field of antibiotics during the past year.

This award honors the name and memory of Rear Admiral Edward Rhodes Stitt, whose long years of distinguished service in military medicine culminated in his appointment in 1920 as Surgeon General of the Navy and Chief of the Bureau of Medicine and Surgery, in which posts he served with distinction for two four-year terms. Admiral Stitt died November 13, 1948, at the Naval Medical Center, Bethesda, Maryland.

He was born in Charlotte, North Carolina, July 22, 1867. After graduating from the University of South Carolina, he obtained his degree from the Medical School of the University of Pennsylvania.

In 1889, he was commissioned an Assistant Surgeon in the Medical Corps of the Navy. He served in many important posts until, in 1917, he was appointed a Medical Director with the rank of Rear Admiral.

Admiral Stitt early interested himself in tropical medicine and, after years devoted to the subject, won an international reputation as an authority in this field. The fruits of these years of study and research are recorded in two textbooks he wrote, which have been published in several editions.

During part of his career, he was an Instructor at the Naval Medical School in Washington, and in World War I, was its Commanding Officer.

Admiral Stitt retired from the Navy in 1931. He was awarded the Navy Cross for his outstanding service in the first World War and held honorary degrees from the Universities of South Carolina, Michigan and Pennsylvania, Jefferson Medical College, and the Philadelphia College of Pharmacy and Science.

Admiral Stitt was President of your Association in 1925, and in 1942 you honored him again with the award of the Gorgas Medal for his accomplishments in tropical medicine.

We, of Pfizer, are happy that our antibiotics award will be associated with Admiral Stitt's name, and we are equally pleased to announce that the recipient of this year's first Stitt Award is another Navy man, Commander John Ridley Seal.

Commander Seal, who was just recently appointed Head of the Communicable Disease Section of the Preventive Medicine Division of the Bureau of Medicine and Surgery, was formerly Officer in Charge and Director of Research, since 1946, at the Naval Medical Research Unit Number 4, U. S. Naval Training Center, Great Lakes, Illinois. It is for his outstanding work on that assignment that we are honoring him tonight. During that period, he conducted rigidly controlled studies of infections of the upper respiratory tract, with emphasis on those caused by streptococci.

Commander Seal and his staff have demonstrated that the oral administration of antibiotics provides an effective, inexpensive means of preventing or aborting epidemics of streptococcal infections and rheumatic fever. While this is of great importance to the Nation in protecting against military manpower loss caused by these diseases, its benefits flow to all men.

This distinguished scientific service in conservation of health and maintenance of our Country's fighting strength is justification, indeed, for Commander Seal's selection as the first recipient of the Stitt Award.

Commander Seal, on behalf of the Awards Committee of the Association of Military Surgeons, and the Pfizer Laboratories Division of Chas. Pfizer & Company, it gives

me great pleasure to present you with this honorarium of $500, a life membership in the Association of Military Surgeons, and this plaque inscribed as follows:

THE
STITT AWARD
to honor the memory of
REAR ADMIRAL EDWARD
RHODES STITT, U. S. N.
is presented through the courtesy of
Pfizer Laboratories, Brooklyn, N.Y.
by the
Association of Military Surgeons
of the United States
to
COMMANDER JOHN RIDLEY
SEAL (MC) U. S. N.
for his meritorious contributions
in the use of antibiotics in the
control of respiratory diseases
Awarded at the
61st Annual Convention
in the city of
Washington, D. C.
December 1, 1954

BAXTER APPOINTS FROHLICH AGENCY

New York, N. Y.—Baxter Laboratories, Inc., of Morton Grove, Ill., has appointed L. W. Frohlich and Co., Inc., as its advertising agency, it was announced here by L. W. Frohlich, president of the agency.

Baxter has been a pioneer and leader in the field of parenteral solutions since 1931. The company is noted for its many solutions, including Travert, and for its accessories and equipment widely used for supplying the electrolyte, caloric and fluid needs of medical and surgical patients.

Among its original developments is the Baxter "Closed System" of vacuum containers and sealed, sterile sets for collecting, storing, transporting, processing and administering blood.

The integrated parenteral program made possible by Baxter's range of solutions, blood donor and recipient equipment, and sets and accessories is used by many hospitals for their infusion and transfusion requirements.

A large staff of medical service representatives is available to help obtain maximum benefits of products to hospitals and the medical profession.

The company's main office and research laboratories are at Morton Grove, Ill. They have other laboratories at Acton, Ont., Canada; Cleveland, Miss., and Johannesburg, South Africa.

FURADANTIN

The first clinical study of blood level determinations for the new urinary antibacterial agent, Furadantin®, have been reported by Dr. Grayson Carroll, associate professor of clinical medicine at St. Louis University, following assays which were unusually delicate because of the low level at which the drug is effective. By contrast, rapid concentration of Furadantin in the urine produces high levels there.

Ten patients who received 200 mg. of Furadantin as an initial dose showed average blood levels of 0.16 mg. per 100 cc. after one hour, 0.11 mg. per 100 cc. after two hours, and 0.08 mg. after three hours. The amount of the drug recovered in the urine of 9 of the patients showed 21.18 mg. per 100 cc. for the first three-hour collection.

Following the initial 200 mg. dose, patients were maintained on 100 mg. of Furadantin every six hours for periods ranging from three to eight days. The average blood level after this period of routine medication was 0.18 mg. per 100 cc. and the highest, 0.26 mg.

"It is evident that the blood levels increase with the continuation of the routine dosage of 100 mg. of Furadantin given every six hours and that a satisfactory blood level was obtained on practically all patients receiving this type of therapy for at least three days," reported Dr. Carroll. He spoke recently to the urology section of the Southern Medical Association at St. Louis.

"The presence of an appreciable amount of Furadantin in the blood explains the favorable clinical results obtained in some conditions other than urinary infections and may widen the therapeutic field of this drug," commented the investigator. He recommended a routine initial dosage of 200 mg. and said that a dose larger than the usual 100 mg. may also be desirable in severe cases after two or three days.

A high concentration of Furadantin in the urine of all patients was found, making it appear that the drug would be "quite effective" in conditions where the urine is retained abnormally.

The blood level determinations were made in collaboration with Dr. Robert V. Brennan and Ruth Jacques.

Lawrence J. Linck, one of the country's best known leaders in the health and welfare field, has resigned as executive director of the National Society for Crippled Chilldren and Adults, it is announced by Edgar Kobak, New York, president. No effective date has been set.

Pending appointment of a new executive director, Mr. Linck will remain in his present post in Chicago. Mr. Kobak, speaking for the Board of Trustees, expressed the hope that Mr. Linck would continue to serve the Society in his voluntary role as secretary and as consultant to the Board of Trustees. Mr. Linck has not announced his future plans.

Mr. Linck's resignation climaxes a ten-year record of achievement marked by phenomenal growth in the number of crippled children helped and the kinds of professional services made available to them. In 1954, a record total of 118,000 crippled persons, of whom 100,000 were children, were given direct care and treatment by the Easter Seal Society nationwide. At the same time, the number of facilities and programs giving these services reached the unprecedented total of 1,000. Under Mr. Linck's direction, the National Society thus became the largest voluntary organization in the world serving the crippled.

Since joining the National Society in 1945, Mr. Linck has expanded the organization from 17 fully accredited state societies to a total of 52 such units including all 48 states, District of Columbia, Alaska, Hawaii and Puerto Rico.

Mr. Linck brought the National Society to the forefront of voluntary health agencies and enhanced both its effectiveness and its prestige during the decade of his service. His achievements have won wide recognition from medical leaders, educators and other distinguished persons who have watched at first hand the progress he has brought about.

Under his leadership, the National Society also created the Easter Seal Research Foundation to undertake special projects to find new ways of helping the crippled.

Mr. Linck is a member of the Board of Directors and Executive Committee of the National Health Council and is the United States representative on the Council of the International Society for the Welfare of Cripples.

Mr. Linck has had a distinguished career in other aspects of health and welfare. Prior to joining the National Society, he was simultaneously for five years, executive director of the Illinois Commission for Handicapped Children and director of the University of Illinois Division of Services for Crippled Children.

NEOHYDRIN FOUND EFFECTIVE IN MODERATE TO SEVERE CARDIAC CASES

Little Rock, Ark.—The oral mercurial diuretic Neohydrin has been found to give an extremely good response even in moderate to severe cases of congestive heart failure where patients' activities are limited.

Three specialists here have reported on a study of 58 patients. Of these, 44 improved without any injections or only occasional ones. Administered in daily continued dosage, Neohydrin practically replaced parenteral therapy. It is "well-absorbed and extremely potent," the authors state.

The study was reported in *American Practitioner and Digest of Treatment* (5:749, 1954). The authors were James C. Doherty, Owen W. Beard, and Habib Sadik of the Division of Cardiology, University of Arkansas School of Medicine.

Many types of heart disease were represented among the cases. In addition to Neohydrin, produced by Lakeside Laboratories, Inc., of Milwaukee, other types of therapy were also evaluated.

"In our hands, other oral diuretic agents, i.e., bromtheophylline, carbonic anhydrase inhibitors, and similar preparations, seem to fail to produce adequate diuresis in patients with congestive heart failure requiring frequent mercurial injections," the authors write. No adverse effect on potassium is noted with Neohydrin.

Convenience and saving time for physician and patient are mentioned as major advantages.

"Simplification of treatment . . . frequently makes continued and conscientious adherence to a necessary regimen much more likely to succeed," the authors point out.

FIND NO MAJOR NEUROLOGIC DAMAGE AFTER 10,098 SPINAL ANESTHESIAS

Philadelphia.—Results of a study of 8,460 patients given 10,098 spinal anesthetics, one of the largest series to receive "spinals" at one hospital, have revealed no instances of major neurological damage after post-operative follow-ups of as much as five years, it is reported in the *Journal of the American Medical Association* (156:1486, Dec. 18, 1954).

The study was made by Drs. Robert D. Dripps and Leroy D. Vandam at the Hospital of the University of Pennsylvania between 1948 and 1951. Based on their findings and other medical data, they term as "unjustified" the tendency "to assume a cause and effect relationship between spinal anesthesia and a variety of complaints, sometimes appearing years after the anesthesia.

"Our experience indicates that the mortality rate following spinal anesthesia is lower than that recorded after general anesthesia in comparable patients undergoing comparable types of operations."

Of the 10,098 spinal anesthetics administered, almost 75 per cent, 7,127, consisted of Pontocaine. The second most frequently employed agent, procaine, was given 1,399 times. A check made at least six months following 8,987 "spinals" disclosed one instance of incapacitating neurological disease. This later proved to be due to a spinal cord condition "that prior to spinal anesthesia had caused no recognizable symptom," the authors state, adding the patient subsequently recovered completely.

Numerically, headache was the most common post-operative complaint. Others included backache; pain and numbness in the buttocks, thighs, legs and feet; and occasional weakness in leg muscles. The majority of complaints, state Drs. Dripps and Vandam, "were transient and disappeared completely with the passage of time."

They attribute the absence of serious neurological damage to the precautions observed in the study. These included: careful selection of patients for a "spinal;" use of a meticulous technique that, long before the anesthetic is given, involves preparation in the way of cleansing and sterilizing equipment; choice of reputable pharmacologic products; use of safe concentrations as the anesthetic mixture; and careful technique in performing lumbar puncture and injecting the anesthetic.

ASPIRIN MOST USED DRUG IN PEDIATRIC PRACTICE

Aspirin is the most commonly used medicinal preparation in pediatric practice, according to a study of 500 infants and children conducted in 1953 at the University of Rochester Medical School and Rochester General Hospital.

The study showed that aspirin and codeine produce the fewest allergic reactions, while penicillin is lowest in producing minor side reactions, with aspirin second lowest.

The infants and children in the test ranged from two months to 15 years of age. Prior to the study, a survey was made to determine the medicinal preparations regularly used by the children. The test data were assembled by Drs. Maximillian Berkowitz, Jerome Glaser and Douglas E. Johnstone.

The data showed that aspirin was used by 450 of the 500 children. Second in order of usage was penicillin, which had been given to 411 children, followed by the sulfonamides, 292; phenobarbital, 260; and codeine, 231. Included in the tabulation were 20 drugs most frequently employed by pediatricians.

Of the 500 children surveyed, the doctors found that 332, or 66.4 per cent, had a prior history of allergic disease. The various drugs included in the study were tested for allergy-producing reactions in all 500 children.

Aspirin and codeine produced the same low over-all incidence of allergic reactions, namely, 1.3 per cent, according to the Rochester team. Among the 18 other preparations, the highest incidence of allergic reaction was 6.8 per cent. In the group of 332 with a prior history of allergic disease, 306 were given aspirin by the investigators. There were no allergic reactions in 300 of these patients. Likewise, no allergic reactions following use of aspirin were observed among all the chil-

dren with no past history of allergic disease. The physicians further reported that 280 of the 411 children who received penicillin were known to be previously allergic and that, when tested, 10 per cent of these 280 showed reactions to the antibiotic.

An analysis was also made of what the doctors called minor side reactions or drug sensitivities, as distinguished from allergic reactions. This phase of the study disclosed that penicillin, with an over-all incidence of 1.4 per cent, produced the fewest sensitivities, followed closely by aspirin with 1.7 per cent. The highest figure for the 20 drugs studied was 14.0 per cent.

Here is a list of the drugs most commonly used: Aspirin, 450 patients; penicillin, 411; sulfonamides, 292; phenobarbital, 260; codeine, 231; aureomycin, 208; pyribenzamine, 188; ephedrine, 141; benadryl, 140; terramycin, 112; other antihistaminics, 77; aminophyllin, 80; epinephrine, 75; other sympathomimetics, 80; opiates other than codeine, 68, atropine, 65; sedatives other than phenobarbital, 57; chloromycetin, 45; iodine, 32; and streptomycin, 20.

The study appeared in *Annals of Allergy* (Vol. 11, No. 5, p. 561).

PFIZER PRESCRIPTION SPECIALTY: TYZINE SPRAY BOTTLE

WHAT THE PRODUCT IS: The nasal decongestant tetrahydrozoline hydrochloride in a yellow 0.1% solution.

WHAT IT'S FOR: The treatment of rhinitis associated with the common cold, hay fever, sinusitis, and nasopharyngitis. Quick and effective in relieving nasal congestion.

HOW ADMINISTERED: Nasal spray.

HOW SOLD: In one ounce plastic squeeze bottle containing 15 cc. of solution.

PRICE TO PHARMACIST: $1.00.

WHO MAKES IT: Pfizer Laboratories, division of Chas. Pfizer & Co., Inc.

DAILY NEED FOR VITAMIN C OFTEN OVERLOOKED

Sixty percent of a group of families studied over a two-year period in Toronto were low in ascorbic acid (Vitamin C) intake. Some families appeared to buy foods rich in ascorbic acid at random, following no plan for meeting the daily recommended allowance for this vitamin. Consistent intakes were noted in only 29 percent of a series of 136 families who were surveyed four or five times at six-month intervals. Citrus fruit, the main source of these families' ascorbic acid, did not increase in price during the period, and no variation due to seasonal factors was noted. The survey was made by Patricia J. Hames and Dr. Elizabeth C. Robertson of the University of Toronto and is reported in the *Journal of the American Dietetic Association* (*30*: 766 (Aug.) 1954).

FRONTIERSMEN IN FOOD PROCESSING

Dr. L. G. MacDowell, research director of the Florida Citrus Commission, and his associates, Dr. E. L. Moore, C. D. Atkins and Eunice Wiederhold Moore, have been designated as "frontiersmen of frozen orange juice concentrate" by Food Processing Magazine, along with nine others who "pioneered in important aspects of this spectacular development." They are: B. C. Skinner, H. S. Madsen, A. L. Stahl, Joe Cross, J. J. R. Bristow, J. L. Heid, Charles Kaufman, R. H. Cotton and the late Norman V. Hayes. The citation appears in the December, 1954, issue of the magazine. Thirty-one out of 100 families reported buying frozen orange juice in October, 1954, according to the U. S. Department of Agriculture. Volume was up 40 percent in a year.

BREAKFAST SHOULD BE SOMEBODY'S BUSINESS

Every family needs a Vice President in Charge of Breakfast, nutrition studies indicate. When no one has this responsibility, breakfast suffers. Particularly apt to be neglected are milk and citrus fruits.

Many children interviewed by New York State (Cornell) Experiment Station investigators made their own breakfast because their parents were not up or had gone to work. Calcium and Vitamin C shortages were generally found in this group. Agricultural biochemists at the Rutgers University College of Agriculture and Experiment Station found that only 49 percent of 610 industrial workers had good breakfasts. Common reasons for poor breakfasts were irregular working hours and no one person at home who takes responsibility. Breakfast should supply from one-quarter to one-third of the day's nutrients.

(Source: Releases from institutions mentioned.)

PLANNING SODIUM-RESTRICTED DIETS

"The enthusiasm for sodium restriction has not always been paralleled with an equal zeal for nutritive adequacy of the regimen," states a report on "Sodium-Restricted Diets," prepared by a committee of the Food and Nutrition Board of the National Research Council. The report includes suggestions for meeting recommended dietary allowances on such a diet. "Adequate supplies of ascorbic acid are assured through the liberal use of citrus and other fresh fruits," it points out. Vitamin A needs may be met through permitted green and yellow vegetables, sweet (unsalted) butter and a small weekly serving of liver. "It is possible to include two cups of milk and still keep the daily sodium intake restricted to approximately 500 mg.," says the committee. Many foods are now packed without added salt or with reduced sodium content. Various spices and herbs can be used to enhance palatability.

BLOOD FILM RELEASED BY E. R. SQUIBB AND SONS TO AMERICAN RED CROSS

Presentation of a 14½-minute color film with sound, *Prescription for Life*, was made to the American National Red Cross for education of the public on the organization's blood program December 9 at a reception at the Hotel Statler, Washington, D. C.

Sponsored by E. R. Squibb and Sons, Division of the Olin-Mathieson Chemical Corporation, the film was presented by John C. Leppart, Executive Vice President of the Olin-Mathieson Corporation. Dr. David N. W. Grant, director of the Red Cross Blood Program, was chairman of the ceremonies, and Ellsworth Bunker, American Red Cross President, expressed the appreciation of the organization in his acceptance remarks.

A preview was shown to guests,

who included physicians and government officials along with personnel from the Red Cross and from the Hartford, Connecticut, Hospital, where hospital scenes were filmed. Aimed especially at groups that make up the bulk of regular blood donors, *Prescription for Life* answers questions frequently asked about what happens to blood after it is donated through the Red Cross blood centers.

A family physician keeps a story thread running, and at the same time brings in valuable scientific information on fractionation processes, which are actually demonstrated along with the refrigeration of blood and plasma.

The film's appeal lies in the variety of situations shown in which blood is urgently needed. A workman at an industrial plant falls from a ladder and is saved from death by a blood derivative. A baby is shown receiving complete relacement of blood because of an RH problem. A mother hemorrhaging in childbirth, an older woman facing major surgery, automobile accident victims, and a boy suffering with third-degree burns make up some of the characters.

Prescription for Life was produced by the William J. Ganz Company, of New York City. Distribution is on a loan basis from the four American Red Cross area offices through local Red Cross chapters. The purchase price is $50.

NEW FILM ON DRUG ADDICTION SEEN AIDING MEDICAL SCHOOLS

Anslinger, Narrator of Movie, Attends First Showing

Members of the medical and pharmaceutical professions saw the premiere in December of a new motion picture designed to alert medical students to the serious social and public health consequences of drug addiction. The film is sponsored by the Federal Bureau of Narcotics and the Department of Pharmacology, University of Maryland School of Medicine.

Titled "Drug Addiction—A Medical Hazard," the 27-minute color film was called a "forceful and dramatic" presentation of the problem by a distinguished invited audience headed by the Hon. Harry J. Anslinger, U.S. Commissioner of Narcotics. Present, in addition to Mr. Anslinger, who narrated the movie, were approximately 500 guests. They included deans and faculty members of medical and pharmacy schools, practicing physicians and military medical personnel.

The film was produced in association with Winthrop-Stearns Inc., pharmaceutical manufacturer. The script was prepared by Dr. John C. Krantz, Jr., professor of pharmacology at the University's medical school, with professional assistance provided by Martin Lasersohn, M.D., Winthrop's executive vice president. Stark Films was the technical producer.

Addressing the gathering prior to the film's showing, Dr. Theodore G. Klumpp, president of Winthrop-Stearns, paid tribute to Commissioner Anslinger's 25 years as head of the Bureau of Narcotics. Nobody has had "a greater influence in stemming the illicit traffic in narcotic drugs throughout the world," he said.

"He has gained ground despite the pressures of international intrigue, the ruthless menace of the underworld, and the conspiracy of Communism to undermine the morale of its enemies with narcotic drugs. Further, he has withstood a maze of bewildering propaganda, confusion and misunderstanding, . . . while retaining his post under four Presidential administrations."

The movie was specially prepared for showing to medical students as an audio-visual teaching tool. It was inspired by an educational program on the dangers of drug addiction initiated 20 years ago at the University of Maryland's School of Medicine by Dr. Krantz. A highlight of the program each year has been a student lecture delivered by Mr. Anslinger.

TEMPERATURE CONTROL FOR ULTRACENTRIFUGE ROTORS

New temperature-control and -measurement system makes possible the continuous indication and automatic control of temperature of operating ultracentrifuge rotors to better than 1/10 of 1 degree C. This new instrumentation, applicable to any Model E Analytical Ultracentrifuge, involves a thermistor embedded in the rotor, electrical connections brought out through mercury-pool contacts, and the control unit and indicator panel which mounts on the existing Ultracentrifuge front panel.

In response to the control unit, a small electric heater beneath the rotor supplies radiant energy as required. When used, the new equipment removes the necessity for the thermocouple and reference-bath system in general use—providing at the same time increased accuracy with simplicity and speed of operation. Provisions can be made for the attachment of an external, continuous recorder.

In function, the unit contains a range control giving ten steps from −10 to +100 C; a precision bridge-balancing potentiometer; a sensitivity control; and a selector switch with positions for "balance," "regulate," "indicate," and "off." The contact-making microammeter simultaneously provides indication and control. (Specialized Instruments Corp., Belmont, Calif.).

ILLUMINATOR

Designed to convert any standard microscope into an integrated unit with a built-in light source employing the Koehler principle, for use in visual microscopy or with existing photomicrography equipment, the new "Ortho-Illuminator B" has just been introduced by Silge & Kuhne of San Francisco.

"The new unit," according to Martin Silge, Technical Director of the optical research and manufacturing firm, "was developed to meet a specific need for a moderately priced illuminator having the same basic characteristics as the standard model Ortho-Illuminator introduced in 1953 in conjunction with the Orthophot photomicrography equipment."

The "B" model is said to provide fingertip control of a full range of light intensity without variation of color temperature; built-in color filters for green, red, or light balanced at 3200° K color temperature; integral field-of-view diaphragm adjusted or centered by convenient controls; and alignment which is permanently maintained even if the microscope is removed or replaced. The unit provides for brightfield, darkfield, phase contrast, polarized light, or fluorescent light work.

Employing the Koehler principle in which maximum numerical aperture is obtained without filament image projection, the unit is claimed to provide optimum resolution dis-

cernible by the human eye with standard Abbe, Aplanatic or Achromatic condensers. The "Ortho-Illuminator B" is also reported to provide an ideal light source for use with any standard photomicrography equipment, for microprojection, and projection drawing.

Literature and price information on the "Ortho-Illuminator B" and accessory equipment may be obtained by writing to Silge and Kuhne, 16th and Carolina Streets, San Francisco 19, California, requesting Bulletin No. 87-12.

PARKE, DAVIS & COMPANY APPOINTS NEW DIRECTOR OF CHEMICAL RESEARCH, DR. LOREN M. LONG

Detroit.—Promotion of Dr. Loren M. Long, 40, to director of chemical research for Parke, Davis & Company was announced recently by Dr. Leon A. Sweet, vice-president and director of research and products development.

Dr. Long, who has been assistant director of chemical research since April, 1952, succeeds Dr. George Rieveschl, Jr., recently named to a new post as scientific assistant to the president, Harry J. Loynd.

Dr. Long shared responsibility for the chemical synthesis of Chloromycetin, the only antibiotic for which a commercial synthetic process has been achieved. He has had charge of the chemical research program in epilepsy which led last January to the announcement of Milontin, a new anticonvulsant for the treatment of petit mal epilepsy. The new compound followed 11 years of study and experimentation in the research laboratories of Parke-Davis, which introduced Dilantin in 1938 for the control of grand mal epilepsy.

Born Jan. 7, 1914, at Dallas, Tex., Dr. Long was graduated from Woodrow Wilson High School there in 1932. He received his B.S. degree in chemistry from North Texas State College in 1937 and a master's degree there in 1939. In 1941, he was awarded a Ph.D. degree in organic chemistry at the University of Texas. He joined Parke-Davis in May, 1941, as a research chemist.

Dr. Long is a member of the American Chemical Society and the American Association for the Advancement of Science.

He and Mrs. Long have three children, Kathleen, 10; Evelyn, 8, and Loren M. III, 5. They live at 1300 Hampton Road, Grosse Pointe, Mich.

GERMAN REPORT ON VITAMINS IN CANCER THERAPY

Frequent improvement in the general status of cancer patients after administration of massive daily doses of Vitamins C and A over long periods is reported by Dr. Erich Schneider of Lahr Hospital in *Deutsche medizinische Wochenschrift* (*79*:584, 1954). Unremovable tumors are often reduced in size, erythrocyte sedimentation rates tend to approach normal, and the patient gains weight. Dr. Schneider describes the procedure as harmless.

ELECTRONIC AIR CLEANER

The hospital of the future will be even cleaner and more sanitary because of the invention of an electronic air cleaner that according to its manufacturer, the Radex Corporation of Chicago, will keep any enclosed area forever dust-free.

This air purifier was developed by Richard R. Cook, President of Radex, after 15 years experimentation. He calls it The Dustronic.

Placed in any room, this cleaner has been proven in laboratory tests to extract up to 99 per cent of all the dust particles in the air.

A series of mechanical and electrostatic filters inside the Dustronic trap the air-borne dirt.

The air first passes through a mechanical filter which captures and holds the larger derivatives of plant, mineral, or animal origin.

Then the air is directed by a baffle, and the finer particles that may evade the mechanical plates, pass through multiple electrostatic collector plates.

Each particle now becomes charged and travels toward a plate which possesses an opposite charge. Due to the design of the collector plates, Cook points out, the turbulent flow of air insures retention of practically all of the undesirable elements in the air.

These collector plates are coated with an adhesive solution which holds such harmful agents as germs, viruses, and pollen, until they are inactivated. The plates can be washed and recoated. The Dustronic is also flameproof and will not produce ozone gas.

Cook sees his electronic device as a great aid in the future to victims of hay fever, asthma, and other allergies who suffer from air-borne irritants.

The Dustronic, Cook says, is not a luxury item, and it can be used in any room. An electronic outlet in the room starts it to work immediately. It will clear the air in a matter of a few minutes of dust, smoke, mists, and germs, Radex tests have shown.

Truly, the Dustronic was born of necessity. Cook's own wife and three children are hay fever victims. Then a manufacturer of small motors, Cook began about 15 years ago experimenting with various types of filters. After trials with no less than 150 models, he finally developed the present unit. He uses it night and day throughout the year in his home in suburban Evanston and in his Chicago office.

Cook's family wouldn't be without it now, he says, and his wife contends she gets double relief from it as she has no allergy trouble while at home, and she does not have to expend time and energy in dusting any more.

LAKESIDE LABORATORIES CONTINUE DYNAMIC GROWTH IN THIRTIETH YEAR

Milwaukee, Wisc. — Lakeside Laboratories, Inc., has reached its thirtieth anniversary.

Its story, particularly the policies that have enabled it to establish one of the most impressive growth records in the pharmaceutical field in recent years, was reviewed on this occasion by Evan P. Helfaer, president.

"We mark our thirtieth anniversary with the hope of new contributions to medicine and pharmacy," Mr. Helfaer said. "The past year has been one of enlarging our scope, and recent months show evidence that the intensive research of the past five years is yielding important results in the way of products even as it explores fields which are new to us." Lakeside has a dramatic new product slated for early introduction.

The company has expanded its plant size by 50 per cent with a new two-story addition to the modern building which it purchased in 1942 for its production facilities and research laboratories.

At the same time, world-wide distribution of its specialties received added impetus; and a new wholly owned subsidiary, Lakeside Laboratories (Canada) Limited, began operations.

The company was founded in 1924. In its early years it was a small regional house. Its history of expansion actually began in 1932 when Mr. Helfaer assumed control and management. In that year, the depth of the depression, the company's volume was $12,000. Now it is well over 450 times as much.

Hormones were the basic interest of the original Laboratories. One of the first to produce natural estrogens, Lakeside established rural stations to collect the pregnant mares' urine from which its scientists processed natural estrones for direct sale to physicians. When synthetic estrogens successfully entered the market, Lakeside diversified its research.

The research department at Lakeside was built up rapidly to develop new products for the needs of modern medicine. Achievements of research were apparent in the report that new prescription products accounted for 28 per cent of the sales volume by 1950.

Under the direction of Dr. Harvey L. Daiell, research continues to receive strong support. A growing number of compounds are being developed and investigated clinically for the treatment of many conditions.

Most successful of all Lakeside's specialties have been in the cardiac field, and the company has attained the pre-eminent position in diuretics. Mercuhydrin, the injectable, is believed to be the largest selling product used in the treatment of congestive heart failure. It is considered the standard for immediate control of salt and water retention in cardiac patients. In 1952, Neohydrin, the celebrated oral diuretic, was introduced. This "little blue pill" has enabled many thousands of individuals to lead more normal lives. Most widely accepted by the medical profession, its prescription sales continue to climb and its reputation has become world wide.

The two diuretics, as well as increasing laboratory research and cooperation with clinical investigators, have provided the basis for Lakeside's claim to "Leadership in Diuretic Research." The company also publishes *Diuretic Review* for the profession, first journal of its kind.

Other products developed by the company's research teams in recent years and widely prescribed by physicians for other diseases, include: the lipotropic line, among them Lipocaps and Lipoliquid for the treatment of chronic liver disease and diabetes; Methyroid for deficient thyroid and metabolic activity; and Obolip for the metabolic control of obesity, representing a striking new approach to the problem.

During the past few years, a significant part of Lakeside's research has been devoted to conditions involving the autonomic nervous system. Earlier this year, the company

introduced an unusual new specialty, the first product of this research program. This is Dactil, a piperidol that relieves pain and spasm in minutes while relaxing the stomach, permitting it to act normally. Distinct from "antispasmodics," Dactil is already widely prescribed.

As a parallel to the long strides taken in new product development and promotion, Lakeside's domestic sales policies have undergone a decisive re-orientation. In 1951, Mr. Helfaer reported that sales to doctors had been steadily reduced to a point where distribution "through-the-trade" accounted for 89 per cent of the total sales. Early in 1954, the transition was completed. Distribution is now exclusively through wholesale and retail drug outlets.

"The company seeks to demonstrate its active interest in its every relationship with the professions, the trade, the employees and the community," Mr. Helfaer explained. Here, for example, are several of the policies and programs that illustrate his point:

The above five-year transition program, as every Lakeside trade policy, is governed by equitable and liberal considerations for all customers.

The pharmacy school program is being enlarged in scope each year. Special emphasis is being placed on educational aids that will help students to learn the relationship between retail and manufacturing pharmacy. Many deans of pharmacy schools have expressed interest in this phase of the program. Grants for basic and clinical research and awards to medical students reflect Lakeside's interest in medical schools.

The authoritative experimental and clinical publication, *Diuretic Review*, is distributed each month to 75,000 physicians, researchers and educators. It reports the latest research, clinical procedures and trends in cardiorenal and electrolyte therapy. This is one of the many ways in which Lakeside serves the medical profession providing material useful in practice and serving clinical investigators. Another is sponsorship of periodic symposia.

A sales training program and continuing instruction in current scientific developments and trade questions help the company's representatives to provide the kind of service that today's pharmacy requires.

A liberal Employees' Profit-Sharing Trust has grown ten times in size in a decade, to well over a half million dollars. Approximately 80 per cent of the employees have the two years of service required for participation in the Trust.

A keen awareness of its responsibilities to its community is shown in the company's participation in many programs. Under the city's new vocational guidance program for high school students, for example, Lakeside was the first company to offer help to youngsters interested in manufacturing and retail pharmacy or chemistry. In the "Junior Achievement" program, which gives teenagers experience in owning and managing a business, Lakeside has supervised the operations of a miniature chemical company.

Market research specialists in the pharmaceutical industry have estimated that sales will increase by 25.6 per cent during the next five years. Lakeside's record in the past few years becomes particularly impressive when compared even with this big national five-year estimate.

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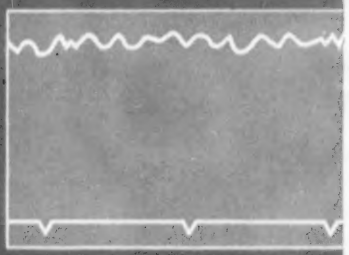
Superior Effectiveness
Increased Convenience

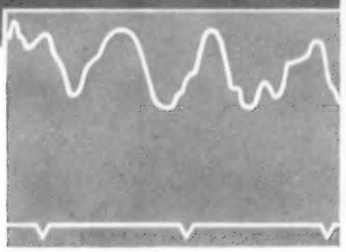
Mucilose®

BLAND BULK HYDROGEL

For Physiologic Bowel Regulation



1. Contractions without Mucilose



2. Contractions 24 hours after ingestion of Mucilose

Mucilose — highly purified hemicellulose from psyllium seed — produces gentle, stimulating, bland bulk, physiologically initiating normal peristaltic waves in the large intestine and at the same time soothing the **irritable colon.**

Superior Effectiveness

Mucilose absorbs as much as 50 times its weight of water which it effectively retains during passage through the bowel, producing a pliable, demulcent stool.

Increased Convenience

To the greater effectiveness of Mucilose is added the increased convenience and flexibility of a variety of dosage forms to meet varied needs:

- **MUCILOSE COMPOUND TABLETS,** Mucilose with methylcellulose; *bottles of 100 and 1000.*

Greater Bulk · Smaller Dosage · Convenient · Easy to Swallow

- **MUCILOSE SPECIAL FORMULA Flakes or Granules**

Also

- **MUCILOSE CONCENTRATED Flakes**

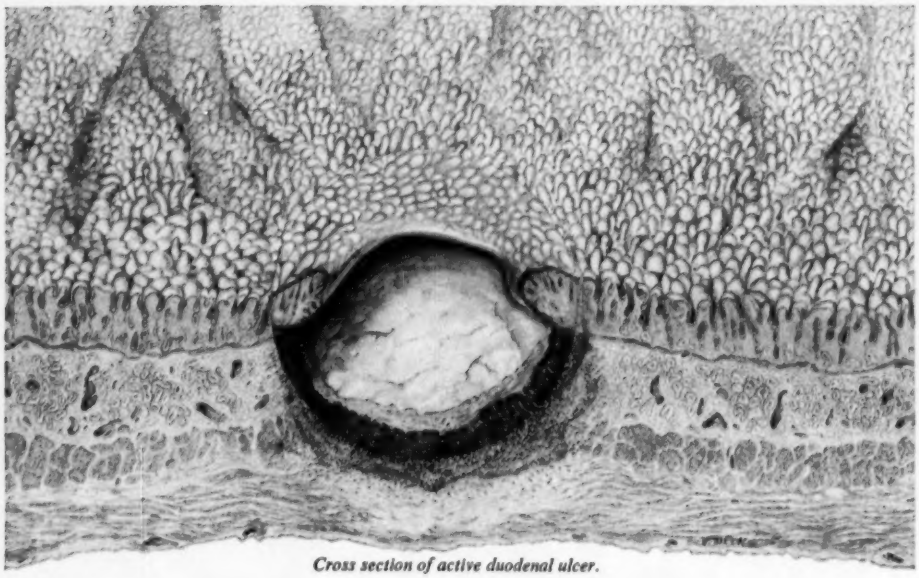
} *in tins of 4 oz. and 1 lb.*

Mucilose should be taken with 1 or 2 glasses of water.

Winthrop-Stearns INC. NEW YORK 18, N.Y. WINDSOR, ONT.

Mucilose trademark reg. U.S. Pat. Off.

PRO-BANTHINE® IN DUODENAL ULCER



Cross section of active duodenal ulcer.

Dramatic Remission of Ulcer Pain

Pain of ulcer is associated with hypermotility; the pain is relieved when abnormal motility is controlled by Pro-Banthine.

"In studying[1] the mechanism of ulcer pain, it is obvious that there are at least two factors which must be considered: namely, hydrochloric acid and motility.

"... our studies indicate that ulcer pain in the uncomplicated case is invariably associated with abnormal motility....

"Prompt relief of ulcer pain by ganglionic blocking agents ... coincided exactly with cessation of abnormal motility and relaxation of the stomach."

Pro-Banthine Bromide (β-diisopropylaminoethyl xanthene-9-carboxylate methobromide, brand of propantheline bromide) is a new, improved, well tolerated anticholinergic agent which consistently reduces hypermotility of the stomach and intestinal tract. In peptic ulcer therapy[2] Pro-Banthine has brought about dramatic remissions, based on roentgenologic evidence. Concurrently there is a reduction of pain, or in many instances, the pain and discomfort disappear early in the program of therapy.

One of the typical cases cited by the authors[2] is that of a male patient who refused surgery despite the presence of a huge crater in the duodenal bulb.

"This ulcer crater was unusually large, yet on 30 mg. doses of Pro-Banthine [q.i.d.] his symptoms were relieved in 48 hours and a most dramatic diminution in the size of the crater was evident within 12 days."

Pro-Banthine is proving equally effective in the relief of hypermotility of the large and small bowel, certain forms of pylorospasm, pancreatitis and ureteral and bladder spasm. G. D. Searle & Co., Research in the Service of Medicine.

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1. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.

2. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinicel Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology *25*:416 (Nov.) 1953.

SEARLE